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SEXUAL PRECOCITY ASSOCIATED WITH HYPERPLASTIC ABNORMALITY OF THE TUBER CINEREUM

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Precocity of sexual development, while constituting a relatively small problem in clinical practice, is nevertheless intriguing from the viewpoint of its etiology and pathogenesis. One of us [1] has emphasized that, while it is usually recognized that hypergenitalism may result from hypergonadism, hyperplasia or tumorous formation of the adrenal cortex and may be associated with pineal tumors in boys, it is little realized that lesions in the brain without involvement of the pineal gland, and particularly without involvement of the hypothalamus, may produce sexual precocity.

Although the mechanism for this remains conjectural, the appreciation that precocious sexuality may be associated with hypothalamic lesions without gross changes in the known endocrine glands and without recognizable evidence of intracranial disease is important.

We studied the case of a 22 month old girl exhibiting precocious sexuality, in whom necropsy revealed what was interpreted as an ectopia of brain tissue between the infundibulum and the mamillary bodies. Our case resembles one reported by Driggs and Spatz,[2] of a boy 33 months old who had enlarged genitalia, erections, pubic and axillary

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1. Bronstein, I. P.: Hypergenitalism in Children, J. Pediat. **14**:203 (Feb.) 1939.

2. Driggs, M., and Spatz, H.: Pubertas praecox bei einer hyperplastischen Missbildung des Tuber cinereum, Virchows Arch. f. path. Anat. **305**:567, 1939.

hair and a bone age of about 15 years. At necropsy an enlargement the size of a hazelnut, located in the midline, was found in the region of the mamillary bodies at the base of the brain. Neuropathologic studies of the brain revealed nothing abnormal except this growth, which was a hyperplastic malformation, probably congenital in origin, with a cellular structure like that of the tuber cinereum.

Le Marquand and Russell [3] reported the case of a boy almost 5 years old with sexual precocity, in whom necropsy revealed a circumscribed tumor attached to the right mamillary body and the left side of the tuber cinereum. The tumor appeared to be a redundant portion of the brain, formed by a developmental error, and was termed a hamartoma.

Gross [4] reported the case of a 2 year old girl with vaginal bleeding, increased bone growth, obesity, hypertension and oliguria in whom an abdominal exploration failed to reveal any growth. After this examination, encephalograms were made, which showed enlarged lateral, third and fourth ventricles and three small nodular masses projecting into the posterior portion of the third ventricle. Death occurred after a cranial exploration, and necropsy disclosed a mass, which was classified as a hamartoma, in the hypothalamus and the floor of the third ventricle.

We shall not review the literature on sexual precocity accompanying hypothalamic tumors, since this has been adequately done recently.[5] In the 17 reported cases, 14 of the subjects were males and 3 were females. In 13 the pineal gland was described as normal, and in the other 4 no reference to it was made. Signs and symptoms ordinarily referable to the hypothalamus were present in some of the patients and entirely absent in others.

Our case is reported to stress the part played by the hypothalamic-hypophysial apparatus in sexual development and to raise some pertinent questions.

REPORT OF A CASE

History.—A. S., born on March 1, 1939, entered the hospital in December 1940 with what was diagnosed as adrenal cortical tumor. The child was apparently well up to the evening preceding her admission, when quite suddenly she began to pass bright red blood from the vagina. She continued to bleed freely, passing clots from time to time. The mother remarked that the girl's breasts had been growing, presumably since birth, and that vulval hair was present. The patient, a full term infant, weighed 6 pounds 7¼ ounces (2,941 Gm.) at birth. The

3. Le Marquand, H. S., and Russell, D. S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumor in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep., 1934-1935, p. 31.

4. Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood, Am. J. Dis. Child. **59**:579 (March) 1940.

5. Weinberger, L. M., and Grant, F. C.: Precocious Puberty and Tumors of the Hypothalamus, Arch. Int. Med. **67**:762 (April) 1941.

feeding and past histories were inconsequential. She had her first tooth at 5 months, sat at 7 months and walked when she was 10 months old. She was the first and only child of young American parents of Polish extraction. The family history showed no instance of endocrine or nonendocrine disturbance. Particular attention was paid to the sexual history of the parents and their kin. There was no similar occurrence in any known living or dead relative. The mental development was normal except for some difficulty in speech, which was attributed to the bilingualism at home. No peculiarities of behavior, sex interest or masturbation were observed in the ward or described by the parents.

Fig. 1.—Photograph of the patient, showing her general physical state and the precocious development of the breasts.

Examination.—The physical examination revealed a 22 month old, well developed and well nourished, nonobese girl with prominent lips (fig. 1). She was proportionate, and the outstanding physical characteristics were the enlarged breasts and the vulvar hair. The gynecologist on rectal examination (with seconal [sodium propylmethylcarbinylallylbarbiturate] anesthesia) found a freely movable mass on the right side, a palpable but normal-sized ovary on the left and a uterus definitely enlarged for a child of this age. The neurologic examination revealed nothing abnormal; there was no vomiting, disturbance of gait, headache or hydrocephalus. The fundi were normal. The dental development was that of a 3 to 4 year old child. The pulse, temperature and respiration were normal. With

forced fluid intake the output of urine collected for hormonal assays on three successive days was 400, 350 and 700 cc., respectively. The blood pressure (9 cm. cuff) was taken on two occasions with the child struggling; the readings were 140 to 130 mm. of mercury systolic and 100 to 90 mm. diastolic. The height was 39 inches (99 cm.), the weight 28 pounds (12.7 Kg.), the upper measurement (pubis to vertex) 49 cm., the lower (pubis to sole) 39 cm. and the bisacromial 13 cm., the circumference of the head (occipitofrontal) 48.5 cm., the circumference of the chest (at the nipples) 51 cm. and the circumference of the abdomen (at umbilicus) 46 cm.

The blood count showed 4,390,000 red cells per cubic millimeter, with 75 per cent hemoglobin, and with 8,200 white cells. The differential cell count revealed 60 per cent lymphocytes, 36 per cent polymorphonuclears and 3 per cent mononuclears, with slight poikilocytosis and moderate hypochromia. Examinations of the urine revealed it to be normal. The Kahn serologic test for syphilis and the Mantoux intracutaneous tuberculin test (1:1,000 dilution) both gave negative results. Chemical examination of the blood showed the following values: cholesterol 192 mg. per hundred cubic centimeters, nonprotein nitrogen 30 mg., creatinine 1.6 mg., calcium 10.25 mg., phosphorus 6.72 mg., ascorbic acid 1.8 mg. and sugar (fasting) 61 mg. The values for sugar after the intravenous injection of 2.2 Gm. of dextrose were: fasting, 71 mg.; after thirty minutes, 59 mg.; after sixty minutes, 70 mg., and after 90 minutes, 75 mg. Studies of the urinary excretion of creatine revealed nothing of significance. Assays of the urine for gonadotropins and estrogens failed to reveal any. Pregnandiol [6] was not recovered from the urine at any time in several forty-eight hour specimens collected by a special apparatus.[7] The usual roentgenograms of the skull showed no abnormalities. However, cephalometry [8] indicated advancement in development, primarily of the jaw but also of the cranial vault, the sinuses and the facial skeleton. Films of the wrist showed little advancement of carpal development. Intravenous pyelograms were normal.

Course.—An exploratory laparotomy was performed, since the findings on rectal examination suggested an ovarian granulosa cell tumor. Nevertheless, considerable credence was given to the possibility of an involvement of the hypothalamic apparatus. At operation no tumors of the ovaries, the adrenal area or any other part of the abdomen were found. Sections of both ovaries were taken and will be described later. After convalescence pneumoencephalography was performed. Complete visualization of the ventricular and subarachnoidal system, including the pontile, interpeduncular and chiasmatic cisterns, revealed normal appearances. After this the patient was discharged, but she was returned a few days later with the symptoms of meningitis, to which she succumbed after nineteen days.

Gross Pathologic Study.—A detailed postmortem examination was made, but only the salient features are recorded here.

The body was that of a well developed and well nourished white girl, 96 cm. long, weighing 12 Kg. The development of the breasts was that of a puberal child. Labial, pubic and axillary hair was present. The clitoris was enlarged.

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6. Genitis, V. E., and Bronstein, I. P.: Pregnandiol Excretion in Female Pseudohermaphroditism, J. A. M. A. **119**:704 (June 27) 1942.

7. Cohen, R., and Blatt, M. L.: Urine Collection for Female Infants, Am. J. Dis. Child. **60**:897 (Oct.) 1940.

8. Bronstein, I. P., and Massler, M.: Roentgenographic Cephalometric Appraisal in Endocrinopathies of Childhood, unpublished data.

The only significant changes in the thoracic and abdominal organs, exclusive of the internal genitalia, were found in the heart and the great vessels. However, the parenchymatous organs exhibited toxic changes attributable to the meningitis. The heart weighed 100 Gm. The left ventricle measured 11 mm. and the right 2 mm. The pulmonary artery measured 40 mm.; its intima contained an occasional single fatty and hyaline plaque. The aorta measured 36 mm.; the intima contained numerous fatty and hyaline plaques, especially in the supravalvular region. The endocardium was thickened and grayish white.

The weights of the various organs (in grams) were as follows: thymus, 4; thyroid, 4; spleen, 50; liver, 650; pancreas, 40; the two adrenals, 8, and the two kidneys, 100. The uterus measured 4.5 by 3 by 1 cm.; the wall was 8 mm. thick, light gray-tan and firm. The endometrium was light tan, 1 mm. thick and smooth. The vagina was light tan, and the mucosa was thrown into shallow folds. The cervix was short and light tan-gray, smooth, with an os uteri externum dilated to 4 mm. in diameter. The fallopian tubes had patent fimbriated ends and were purplish red. The walls were thin and the mucosa smooth. The remaining portion of the right ovary measured 1 cm. in diameter and was light gray-tan and firm, with a few small cysts, which measured up to 2 mm. in diameter; the left ovary was similar.

The brain was removed and after brief inspection, which revealed a leptomeningeal exudate at the base, was placed in solution of formaldehyde.

Formaldehyde-Fixed Brain: The leptomeninges over the convexity of the brain were hyperemic and appeared to hold an excessive amount of fluid but were everywhere transparent. At the base, the meninges were thickened and contained a farinaceous, granular material which obscured the landmarks of the third nerve, pons and cerebellopontile angle. Serial coronal slices through the brain, and cross sectional slices through the brain stem and cerebellum revealed no marked changes, except for a slight dilatation of the ventricular system, the granulations in the basilar meninges and a small tumor-like formation in the midline near the infundibulum. In gross appearance the pineal body showed nothing abnormal.

At the base of the brain, in the region of the tuber cinereum, just posterior to the infundibulum, there was a midline globular grayish white, glistening mass about 4 mm. in diameter, which at first observation appeared to represent a fusion of the mamillary bodies. However, a subsequent coronal section revealed the presence of the mamillary bodies just behind this knob of tissue, which itself appeared not unlike them in color and consistency (fig. 2).

Microscopic Examination.[9]—Brain: Histologic examination revealed the presence of a purulent leptomeningitis (chiefly basilar in situation), marked by an exudate containing polymorphonuclear leukocytes, many arachnoidal macrophages, occasional histiocytes and considerable fibroblastic proliferation. A ventriculitis was also found, marked by perivascular infiltrations with round cells, polymorphonuclear leukocytes and even plasma cells underlying the ependymal surface. In some regions, as in the fourth ventricular floor, the cellular infiltrations extended into the brain tissue itself.

The thin coronal slice through the region of the hypothalamus containing the knoblike formation which resembled fused mamillary bodies was embedded in paraffin and sectioned serially. The tumor-like structure was found to consist of brain tissue containing ganglion cells, axis-cylinders and very few myelinated fibers (near the surface) in a glial stroma richly supplied with capillaries. In most sections it was entirely surrounded by its own thin covering of inflamed

9. Dr. Arthur Weil assisted in the histologic study.

leptomeninges, and in sections through part of its caudal extent it appeared in juxtaposition with a narrow infundibulum-like pedicle at a point situated above it. This stalk showed the normal histologic structure of the neural hypophysis, with glial tissue surrounding a tiny central cavity lined by ependymal cells, except near its apparent junction with the tumor-like mass below, where it became rudimentary; the actual connection was a meningeal band. It was presumed that this stalk was connected with the tuber cinereum, but, unfortunately, because the block was sectioned from each (rostral and caudal) surface, some of the sections of the midportion were lacking, and the actual origin of the stalk could not be confirmed. The ganglion cells of the tumor-like formation were found in irregular groups; for the most part they were small, pyramidal or unipolar

Fig. 2.—Caudal surface of a thin coronal slice revealing a tumor-like formation (*T*) between the infundibulum (*I*) in front and the mamillary bodies (*M, M*) behind. The thalamus (*Thal*), the third ventricle (*III*) and the corpus callosum (*CC*) are indicated. × 2 (approximately).

forms, without clearly demonstrable Nissl substance, but in an occasional medium-sized, pyramidal or multipolar cell Nissl bodies could be recognized (fig. 3). The ganglion cells present were apparently diseased, presumably from the toxic effects of the meningitis, in addition to being immature; and in neighboring regions of the hypothalamus the picture of acute ganglion cell disease was often noted. It was difficult to differentiate many of the ganglion cells from altered glial cells (*gemästete Glia*) that were also present. The glial nuclei were for the most part like those of astrocytes or microglia. The Holzer stain revealed a rich network of glial fibers in certain parts of this abnormal body.

In general, the histologic makeup of this tumor-like formation resembled the primitive cortical structure of the tuber cinereum. Whether this was a gangliogliomа, a heterotopia of the tuber cinereum or a hamartoma must be considered. The lack of invasiveness and of disorderly growth and the predominance of glia over ganglion cells speak against a ganglioneuroma. The complete mantle of

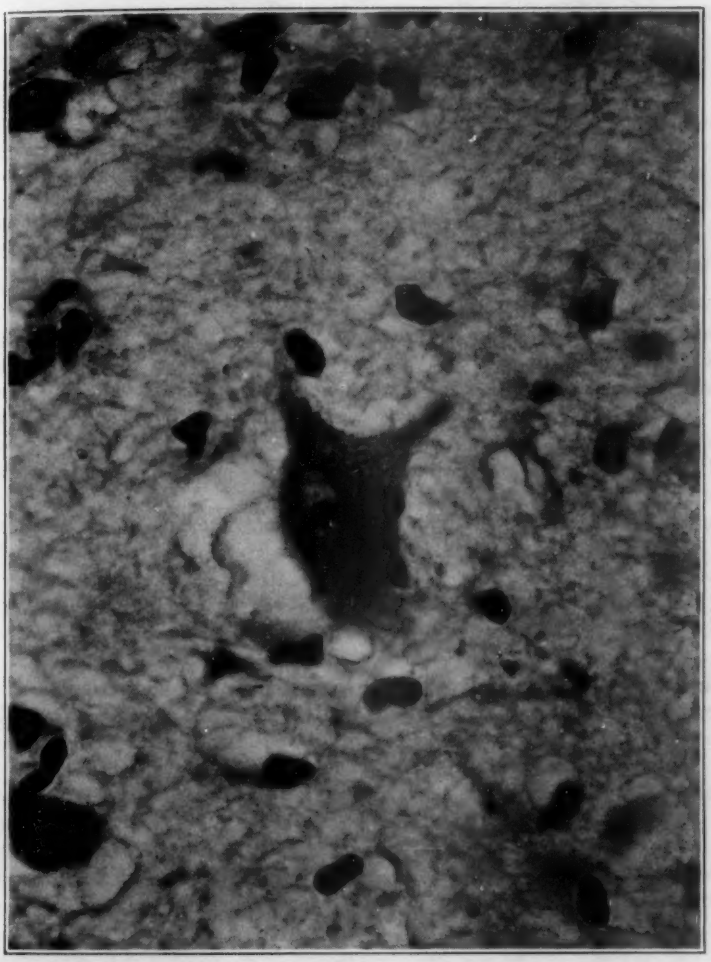

Fig. 3.—Photomicrograph of a section of the tumor-like formation showing one of the larger ganglion cells. Cresyl violet; × 943.

leptomeninges and the smooth, regular surface formation of the mass are inconsistent with the interpretation of pseudoheterotopia (in the sense of postmortem mechanical deformation). In many respects this hyperplastic abnormality could be considered a hamartoma (in the sense of Albrecht's definition).

Sections through the median eminence (that portion of the neurohypophysis of purely glial structure in the median plane of the floor of the third ventricle, from which the infundibular stalk arises) revealed a richly cellular region comprised of elongated bipolar cells in which inflammatory perivascular infiltrations

could be seen underlying the ependymal surface. The general appearance of this region suggested a hyperplastic state of the median eminence.

Pituitary Gland: This was fixed in solution of formaldehyde, embedded in paraffin and stained by a special method.[10] Several sections revealed that there were groups of eosinophils with the chromophobes in the background. The basophils for the most part were close to the capsule, while the eosinophils were in the central portion of the gland. The cells were swollen and granular, and the interstitial blood vessels were dilated and congested. A differential count of the three types of cells revealed 60 per cent eosinophils, 30 per cent basophils and 10 per cent chromophobe cells. The posterior lobe of the gland showed no changes.

Heart: The epicardium was thickened. The muscle fibers were swollen and hypertrophied, and the cytoplasm was granular with indistinct striations. The nuclei were oval to barrel shaped. There was a slight to moderate increase of interstitial fibrous tissue, especially around the blood vessels and also in places between the individual muscle fibers. Sudan III stain revealed no deposition of fat.

Breast: There was found a stroma composed of wavy, collagenous, fibrous tissue, embedded in which were groups of glands. There was an extreme hyperplasia of the epithelium of the glands, some of which showed pronounced cystic dilatation, with an amorphous debris in the lumen.

Skin: The skin of the labia minora and labia majora showed moderate hyperkeratosis and acanthosis, with congestion of the capillaries and blood vessels in the subcutaneous area. There was a slight infiltration of round cells near the basal cell layer. The skin of the suprapubic and axillary areas showed a mild hyperkeratosis, and there were many hair follicles and sebaceous glands present.

Uterus: The wall was composed of interlacing bundles of smooth muscle fibers and fibrocytes with dilated and congested interstitial blood vessels. The endometrial stroma was mildly edematous, with slight infiltration of round cells. The glands were moderately large, with a low columnar epithelium. A few of the glands showed some tortuosity. There was a small amount of amorphous debris over the surface of the mucosa.

Ovaries: The ovaries both showed numerous primordial ova embedded in a fibrous tissue stroma with dilated and congested interstitial blood vessels. There were a few small follicular cysts lined by cuboidal epithelium. The surgically removed portions of the ovaries were similar.

Anatomic Diagnosis: The diagnosis was: (1) purulent basilar meningitis (pyocyaneus); (2) hyperplastic abnormality (hamartoma?) in the hypothalamic region; (3) sexual precocity, with enlargement of the breasts, labia majora, labia minora and uterus; (4) relative eosinophilic hyperplasia (?) of the pars distalis hypophyseos; (5) eccentric hypertrophy of the heart with dilatation of the right cardiac chambers and endocardial sclerosis; (6) hair in the suprapubic, axillary and labial regions; (7) cloudy swelling of the liver, kidneys and myocardium; (8) passive congestion of the liver, kidneys and lungs (all lobes); (9) infectious hyperplasia of the spleen; (10) slight interstitial fibrosis of the pancreas; (11) partial surgical removal of both ovaries; (12) old laparotomy scar.

COMMENT

The differential diagnosis lay between an ovarian tumor of the granulosa cell type and some involvement of the hypothalamic region.

10. Bayley, J. H.: Differential Staining Methods for Formalin-Fixed Human Pituitary, J. Path. & Bact. **49**:261, 1939.

The absence of any intracranial symptoms before pneumoencephalography was evidence that there were no pressure effects. Vickers and Tidswell [11] reported sexual precocity and uncontrollable behavior in an 8 year old boy with no other evidence of intracranial involvement. At necropsy a nonobstructing tumor the size and shape of a walnut was found occupying centrally the floor of the third ventricle and projecting freely into it. Apparently, rather large, slow growing tumors can be present in this area without the production of cerebral symptoms.

The difficulty of making a definite diagnosis in a case like ours or in similar cases is obvious. The important thing is to bear in mind the possibility of hypothalamic involvement. In a former experience with hypergenitalism [1] complete investigation failed to reveal the etiologic factor, and therefore hypothalamic involvement was seriously considered. This patient exhibited excessive excretion of urinary gonadotropins as well as of adult androgens.

At that time one of us [1] suggested the similarity in picture between the condition of this boy, who exhibited excessive amounts of urinary gonadotropins, and the changes simulating sexual precocity in boys undergoing therapy for cryptorchidism with excessive amounts of chorionic gonadotropin. An exhaustive study [12] is in progress of a boy 3½ years of age with great sexual precocity and spermatogenesis who exhibited no intracranial signs. The encephalogram revealed nothing abnormal, and the urinary gonadotropins were in excess of normal. Here again we suspect hypothalamic involvement.

Whether the mass found in our patient was merely incidental or was the cause of the precocious sexuality is of great interest. In reviewing all the cases of precocious sexual development associated with tumor of the hypothalamus, it is rather suggestive that, in the absence of anything else, such a growth may be the cause of the hypergenitalism. The relation of experimental lesions of the hypothalamus to sexual functions is recorded in the literature. In our case the lesion was small and was just rostral to and below the mamillary bodies, fulfilling in many respects the conditions of an experiment. In all the verified cases of sexual precocity with hypothalamic lesion, the floor of the third ventricle was directly or indirectly affected; and in those cases with a relatively small lesion, the midline area between the infundibulum and the mamillary bodies was involved.

The mechanism whereby a growth like this produces precocious sexual phenomena is not known. Various hypotheses have been advanced including the assumption that the growth possesses inherent hormonal

11. Vickers, W., and Tidswell, F. M. B.: A Tumour of the Hypothalamus, M. J. Australia **2**:116, 1932.

12. Bronstein, I. P.: Unpublished data on hypergenitalism.

functions.[13] The theory that the tumor alters the pathways which may extend to the pituitary gland and thus brings about endocrinologic manifestations indirectly through this gland has also been proposed. Weinberger and Grant [5] have suggested that a tumor of the posterior portion of the hypothalamus may interfere with nerve impulses to the pars distalis hypophyseos, resulting in excess production (or release) of large amounts of gonadotropic substance, which, in turn, stimulates the ovaries or testes to hyperactivity. Our patient had no abnormal amounts of gonadotropic or estrogenic hormones. Our 2 male patients, who, by exclusion, we believe may fall into a similar category, both had excessive amounts of gonadotropic substance. It has also been suggested [4] that a vascular congestion may be set up by the extraneous mass and that this may affect the pituitary gland. Most speculations embody the idea that the effects resulting in the sexual precocity are mediated in some way through the anterior lobe of the pituitary gland.

The discovery of this growth in our patient was a mere accident, and such lesions can easily be overlooked unless one is aware of their occurrence. The question arises whether continued life and reasonable longevity may not be compatible with these growths. We may assume this from reports [14] in which sexual precocity was found in a father and 2 sons as well as in other members of the family.

CONCLUSIONS

Sexual precocity in a 22 month old girl is reported.

Death occurred through an accidental meningitis,[15] and necropsy revealed a small tumor-like mass beneath the floor of the third ventricle, between the infundibulum and the mamillary bodies. The structure of this hyperplastic malformation was not unlike that of the tuber cinereum.

Precocious sexual development may be associated with a tumor or a hyperplastic abnormality of the hypothalamic apparatus. The mechanism responsible for this phenomenon is conjectural and its determination opens an interesting field for experimentation.

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13. That nerve tissue may have secretory functions is attested to by Geiling's work on the posterior lobe of the pituitary and by the studies of the Scharrers (Scharrer, E., and Scharrer, B.: Secretory Cells Within the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. [1939] **20**:170, 1940).

Histologic examination of the tumor failed to reveal cells like those of the supraoptic and paraventricular nuclei to which the Scharrers ascribe secretory functions.

14. Rush, P. H.; Bilderback, J. B.; Slocum, D., and Rogers, A.: Pubertas Praecox (Macrogenitosomia), Endocrinology **21**:404, 1937.

15. The meningitic aspects are being reported by Drs. Levinson, Perlstein and Kerman.

TREATMENT OF GONORRHEAL VULVOVAGINITIS WITH ESTROGENS

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The discovery of the organism responsible for gonorrheal infection in the genitalia by Neisser in 1879 established for the first time a sound basis for the investigation of genital infections. Soon thereafter it became recognized that some of the genital discharges in prepubertal girls were likewise gonorrheal in origin. This condition in young girls remained a distressing problem for the patients and their mothers, the physicians and the school authorities. Treatment of the condition through the next half-century was entirely symptomatic and empiric and produced little effect. Many therapeutic measures were tried and discarded, but it still required several months to several years to effect a cure in these unfortunate young girls.

After the isolation of estrogens by Allen and Doisy,[1] the effect of such agents on the genital organs of experimental animals and human subjects was intensively studied. In 1917 Stockard and Papanicolaou [2] reported the estrus cycle of the guinea pig. This cycle was confirmed in 1922 for the mouse by Long and Evans [3] and independently by Allen and Doisy,[4] who established it as a means of bioassay for estrogens. In 1928 Allen [5] reported that similar changes in the vaginal epithelium could be produced in immature animals by the use of estrogens. It had long been known that with the establishment of puberty and the cornification of the vagina in these infected young girls the vulvovaginitis usually subsided. It remained for Lewis [6] in 1933, to put these two ideas

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1. Allen, E., and Doisy, E. A.: Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification, and Action in Test Animals, J. A. M. A. **81**:819 (Sept. 8) 1923. Doisy, E. A.: Am. J. Physiol. **90**:329, 1929.

2. Stockard, C. R., and Papanicolaou, G. N.: Am. J. Anat. **22**:225, 1917.

3. Long, J. A., and Evans, H. M.: Oestrous Cycle in the Rat and Its Associated Phenomena, Memoirs of the University of California, 1922, vol. 6, p. 1.

4. Allen, E., and Doisy, E. A.: Am. J. Anat. **30**:297, 1922.

5. Allen, E.: J. Morphol. **46**:479, 1928.

6. Lewis, R. M.: Am. J. Obst. & Gynec. **26**:593, 1933.

together and to begin a study of the therapeutic use of estrogens in cases of prepubertal gonorrheal vulvovaginitis. Failures were frequent, and the search for improved methods of treatment continued. The introduction of sulfanilamide and its derivatives in the treatment of this condition has aroused a new interest, but they too have proved somewhat disappointing. The results have not been entirely satisfactory, and there has been a reasonably high incidence of toxicity on continued use; relapses are not infrequent.

There is one phase of Lewis' original work which has been frequently forgotten, and it is the greatest single factor responsible for failure of the estrogen therapy of gonorrheal vulvovaginitis. This is that "the vaginal epithelium must be cornified." In their enthusiasm to popularize this form of therapy the pharmaceutic houses have placed in the hands of the physician suppositories, ampules, capsules, etc., with instructions that "one a day will chase the clap away." They have forgotten entirely the well known concept of personal variation with regard to the dosage of any therapeutic agent.

Fortunately, cornification of the vaginal epithelium is very easily detected—more easily by far than a urinalysis or a blood count is made. The basal cell of the vaginal epithelium is a round cell with a large dark-staining, central nucleus. In the absence of estrogenic stimulation this type of cell appears in the vaginal mucus together with a variable number of leukocytes. In the presence of infection frank pus is seen. As the basal cells are matured by estrogen (either naturally or as the result of treatment) they become larger and the cytoplasm is clearer. The nucleus becomes smaller and pyknotic and may even disappear. The edges of the cell become darker and begin to curl. The ratio of the size of the nucleus to that of the basal cell is about 1:3, while in the cornified cell it is 1:10 or 1:12. In the process of cornification the pus disappears, and only an occasional leukocyte is seen. The differences in these cells are demonstrated in figures 1, 2 and 3.

During the past several years a number of articles have appeared on the subject of treatment with estrogens.[7] The authors have been

7. (*a*) Cohn, A.; Steer, A., and Adler, E. L.: J. Pediat. **20**:4, 1942; (*b*) Am. J. Syph., Gonor. & Ven. Dis. **25**:329, 1941. (*c*) Rice, J. L.; Cohn, A.; Steer, A., and Adler, E. L.: Recent Investigations on Gonococcic Vaginitis, J. A. M. A. **117**:1766 (Nov. 22) 1941. (*d*) Mukherjee, C. I.: J. Obst. & Gynaec. Brit. Emp. **47**:275, 1940. (*e*) Daffinee, R. W.: Arch. Pediat. **57**:295, 1940. (*f*) Holmes, J. W.; Jones, J. A.; Einhorn, N. H., and Wikler, L. A.: J. Pediat. **19**:70, 1941. (*g*) Russ, J. D., and Collins, C. G.: Treatment of Prepuberal Vulvovaginitis with New Synthetic Estrogen: Preliminary Report, J. A. M. A. **114**:2446 (June 22) 1940. (*h*) Te Linde, R. W.: Treatment of Gonococcic

(Footnote continued on next page)

divided in their opinions as to its value. Uniformly, those physicians who have found the use of estrogens unsuccessful have disregarded the basic principle of estrogenic therapy. They have presented charts showing that a certain number of patients were treated with estrogens with a varying but high incidence of failure. None of these authors [8] made any statement as to the degree of cornification obtained. Frequently the amount of estrogen used was not stated; in the few cases in which dosage was mentioned, it was ridiculously low.

It is the purpose of this report to present a short series of cases (13) and to point out the importance of individualization of treatment. I wish to emphasize several features of the clinical management of patients with gonorrheal vulvovaginitis which if followed will give a high incidence of cure. In addition, my colleagues and I have treated 6 patients with nonspecific vaginitis who were referred to us with the diagnosis of gonorrhea. Attention is particularly called to the following protocols of 5 patients. They have been selected because they demonstrate clearly the common reasons for failure in the management of such patients.

REPORT OF CASES

CASE 1.—A girl consulted her physician because of a vulvovaginitis which was considered nongonorrheal and which had been treated with various antiseptic irrigations for three months. After this she was given sulfapyridine; the amount is unknown. There was temporary improvement followed by complete relapse. The patient consulted a second physician,[9] who made the diagnosis of gonorrheal vaginitis and gave the patient sulfathiazole; there was prompt improvement. The drug was discontinued in two weeks, with subsequent return of symptoms and a positive smear ten days later. The patient was again given sulfathiazole, but a rash, fever and vomiting developed. Administration of this drug was discontinued, and use of estrogen suppositories was begun. There was early prompt improvement. After two weeks the discharge returned, but no gonococci could be seen in the smear. The patient was then referred to me for advice. On examination there was residual but minimal evidence of an inflammation about the vulva and a white nonpurulent discharge. The smear showed the epithelium to be well cornified, and no gonococci or leukocytes were present. It was felt that this patient had had adequate estrogenic therapy and that the discharge was probably due to local sensitivity to the suppositories; estrogenic therapy was continued by oral administration. The discharge disappeared in forty-eight hours. Six months later, without therapy for five months, the smears were negative for gonococci and there was no discharge.

Conclusion.—Sensitivity to the vehicle of the estrogen may produce an apparent failure.

Vaginitis with Estrogenic Hormone: Further Studies, ibid. **110**:1633 (May 14) 1938. (*i*) Witherspoon, J. T.: Treatment of Gonorrheal Vulvovaginitis in Childhood with Ovarian Follicular Hormone: Series of Cases in Which Treatment Was Unsuccessful, Am. J. Dis. Child. **50**:913 (Oct.) 1935.

8. Footnote 7 *a*, *b*, *c*, *d*, *e* and *i*.

9. Through courtesy of Dr. Ruth Burroughs, Omaha.

CASE 2.—A 4 year old girl came to the dispensary with a history of vaginal discharge and recurrent enuresis. Examination showed a purulent vaginal discharge and inflammatory changes about the vulva. An area of protuberant mucous membrane, which was thought to be edematous hymen, was seen in the introitus. Smears were positive for gonococci. The patient was given a fourteen day trial of sulfathiazole without improvement, and estrogenic therapy was then started. Vaginal smears promptly revealed cornified epithelial cells. Purulent discharge continued, and vulvar smears continued to show infection. After six weeks of intermittent cornification of the vaginal epithelium as shown in smears and vulvar smears still positive for gonococci, the patient was seen by me and examined under anesthesia. At this time it was discovered that she had a gonorrheal urethritis and a large urethral polyp. Separate vaginal smears were negative for gonococci. The polyp was removed by cautery. Estrogenic therapy was continued for one more week to prevent the possibility of reinfecting the vagina, and the patient was again given sulfathiazole. In the course of two weeks her urethral and vaginal smears were negative and the discharge was apparently gone. She still shows no evidence of gonorrheal infection, four months later.

Conclusion.—Gonorrheal urethritis cannot be cured with estrogenic therapy.

CASES 3 and 4.—Two sisters, V. and M., were admitted to the dispensary with a vaginal discharge. On examination there was clinical evidence of inflammatory changes about the vulva, and bacteriologic studies revealed the infection to be caused by the gonococcus. These two girls had been treated for several months prior to admission with sulfonamide compounds. Estrogenic therapy was started, and inasmuch as there was only about 5 pounds (2.3 Kg.) difference in body weight, they were given the same dose. V. acquired a well cornified vaginal epithelium in ten days, and the gonococci disappeared from her smear. M., on the other hand, still showed a basal type of epithelium and many leukocytes and gonococci. Her dosage was progressively increased, and full cornification was not obtained until twenty-eight days from the beginning of treatment. She required two and one-half times as much estrogen as her sister. Full cornification of the vaginal epithelium was maintained in both girls for one month, and therapy was discontinued. Both children were free of infection at check-up examination six weeks and three months later.

Conclusion.—The number of units of estrogen required for vaginal cornification varies widely. One must adapt the dosage to the patient.

CASE 5.—A girl entered the dispensary with a diagnosis of gonorrheal vaginitis, because of the presence of a similar infection in the mother. On examination the findings were typical of gonorrheal vulvovaginitis and slides showed gonococci. Estrogen therapy was started but was discontinuous for about two months. As soon as partial cornification was obtained, the discharge subsided, and the patient did not return to the clinic. She was then given a preparation for oral administration, which she used at home for six weeks. Smears then showed well cornified cells for the first time, and the gonococci had disappeared. The patient was free of infection two months later.

Continuous vaginal cornification is essential to success.

COMMENT

This report covers a very small series of cases, namely, 19: 13 of gonococcic and 6 of nonspecific vaginitis. In each of these cases sulfanilamide or one of its derivatives had been tried for varying lengths of time. In each case the drug had failed to cure the vulvovaginitis. Inasmuch as the therapy was carried on by various persons without laboratory control, I am well aware that these results do not represent the true effectiveness of these drugs in the treatment of this condition. All of the children treated with estrogen were cured bacteriologically and

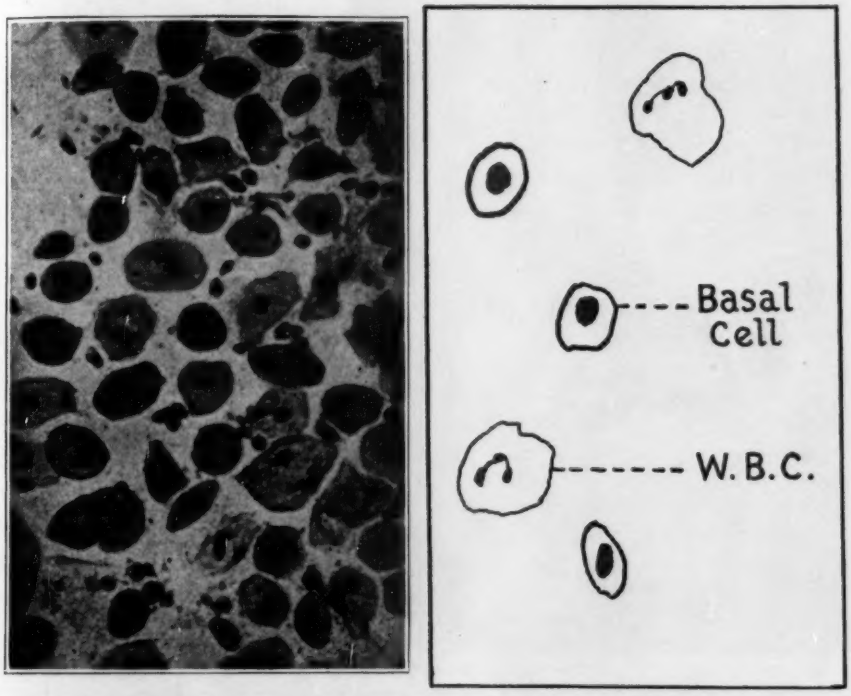

Fig. 1.—Photomicrograph of a vaginal smear made during deficiency of estrogen, showing the basal cells and leukocytes. This condition is normal before puberty. (From Shorr, E. J.: J. Pediat. **19**:327, 1941.)

clinically. This unusually high incidence of cure following the use of estrogenic therapy is likewise probably misleading, for undoubtedly in a larger series there will be cases in which estrogenic therapy will also fail. It is my opinion, however, that if the cases are properly managed (vaginal cornification maintained continuously for four weeks) the percentage of failure will be small.

In discussing the control of therapy by cornification of the vaginal epithelium, it is perhaps wise to outline the procedure necessary for obtaining and reading these slides, although it is so simple that one

hesitates to describe it. Many elaborate schedules have been published in the literature; but in my opinion these are not necessary, for with a very brief experience one can learn to recognize the necessary changes of the appearance of the cells. The following method seems adequate:

The vulva is cleansed with moist cotton to remove accumulated discharge. A small cotton applicator is then moistened with sodium chloride solution and gently introduced into the vagina. This is withdrawn and smeared on a clean glass slide and allowed to dry. The smear is lightly fixed with heat or with acetone alcohol, and the slide is then stained with any of the simple stains and allowed to dry

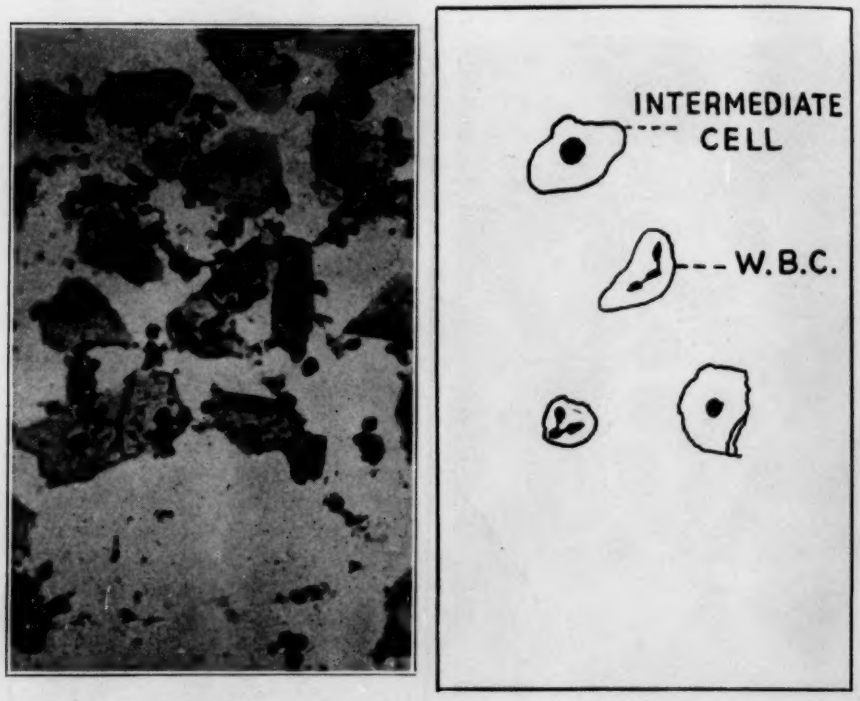

Fig. 2.—Photomicrograph of a vaginal smear made during moderate estrogenic stimulation. The leukocytes are disappearing and the basal cells are larger. (From Shorr, E. J.: J. Pediat. **19**:327, 1941.)

(one may use the Gram stain and thereby determine both the degree of cornification and the presence of the gonococcus). There are other more elaborate stains and classifications published in the literature to which the reader is referred.[10] The change in the microscopic appearance, as a basal cell becomes a cornified cell, is so marked that special staining characteristics are not necessary to differentiate them. Figures 1, 2 and 3 demonstrate these changes.

10. (*a*) Papanicolaou, G. N., and Shorr, E.: Am. J. Obst. & Gynec. **31**:806, 1936. (*b*) Rubenstein, B. B.: Endocrinology **27**:843, 1940. (*c*) Shorr, E.: Science **91**:579, 1940. (*d*) Hartman, G. C.: Am. J. Physiol. **95**:13, 1930. (*e*) Mack, H. C.: Harper Hosp. Bull. **1**:54, 1942. (*f*) Geist, S. H., and Salmon, U. J.: Am. J. Obst. & Gynec. **38**:392, 1939. (*g*) Shorr, E.: Science **94**:545, 1941.

Estrogens were given parenterally in these cases. The injectable preparations were selected in order that frequent observation and careful control of the patient could be obtained. Only a few of these patients were treated with diethylstilbestrol, and this was usually given by injection. With the release of this drug to prescription sale, the physician has at hand a much more convenient method of administering estrogens. It will still be necessary, however, to control the dosage by the use of vaginal smears. When diethylstilbestrol is administered orally, the mother can be taught to obtain the smears; she should take them to the physician for staining and interpretation.

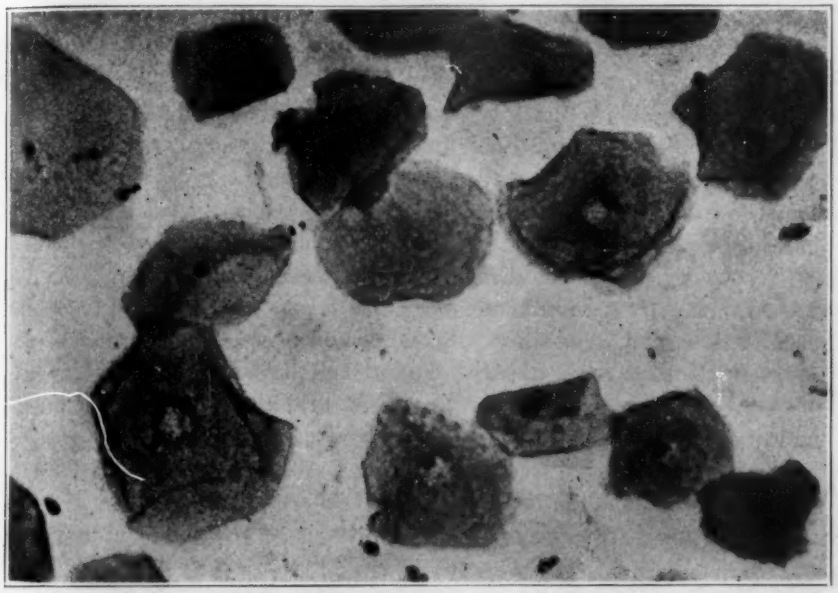

Fig. 3.—Epithelial cells of the vagina during estrogen saturation. Cornification is now complete. The amount of estrogen necessary to bring about this state is the "physiologic unit." (From Shorr, E. J.: J. Pediat. **19**:327, 1941.)

There is one additional comment that should be made. It is observed at once that no statement is made regarding the type of estrogen or the dosage recommended. I feel that it is impossible to recommend a product or dosage in terms of rat units, international units or milligrams for these patients because of the personal variation in requirement.[11] For this reason we have used a new unit, the "physiologic unit,"

11. In estimating the doses for these patients, milligram equivalents of estrone were used, on the basis of 0.1 mg. = 1,000 international units. The range of dosage varied from 0.2 to 1.0 mg. given one to three times a week. The average patient required a total of approximately 1.5 mg. (15,000 international units) before cornification became apparent.

which is the amount necessary to cornify the vagina. A brief pause for reflection convinces one of the necessity for this step. The adoption of this unit has led us to use much larger doses [10] than are usually recommended, and one might expect complications from this therapy. Two complications are to be feared: (1), the maturing of the genitals with the development of salpingitis, and (2) a permanent upset in the endocrine system of these young girls.

In regard to the former, this complication did not occur in these patients or in an untabulated personal experience elsewhere. I have established a rule that estrogenic therapy shall not be used after a girl is 10 years of age or if there are signs of early menarche (pigmentation and enlargement of the breasts, pubic and axillary hair or enlargement of the clitoris or labia). Such patients will usually have cervicitis and not vaginitis, and all will show varying degrees of vaginal cornification. If this rule is followed, salpingitis should be extremely rare, for either it requires three to four times the amount of estrogen to enlarge the uterus and open the tubes as it does to cornify the vagina or the dosage must be maintained for a long period. Mild transitory changes in the breasts, similar to those seen in the newborn, are not uncommon.

As far as subsequent disturbance in the endocrine system is concerned, one can only speculate, since this form of therapy has been in use for less than ten years. From personal observations, a few of the patients have subsequently matured and have apparently initiated a normal function. Hartman [10d] in 1930 demonstrated the transitory nature of changes brought about in the monkey by the administration of estrogens. Experience with adult patients and women undergoing the menopause points to the temporary effects of estrogen; hence one should not expect any subsequent disturbance in the patient's endocrine balance.

SUMMARY AND CONCLUSIONS

A series of cases of gonorrheal vaginitis treated successfully with estrogens is presented.

The basic principles of estrogen therapy (cornification of the vagina and individualization of the treatment) are reviewed.

A new unit for estrogen therapy, the "physiologic unit," is suggested.

The incidence of cure with this form of therapy is gratifyingly high, and complications are very low (none in this series).

Drs. J. A. Hauske, C. A. Tompkins, P. N. Morrow, R. Burroughs, G. J. Klok and J. L. Gedgoud, of the pediatric staff, cooperated in furnishing the clinical material, making examinations and directing the therapeutic measures.

The estrogenic material used in this study was furnished by the Smith Dorsey Company, Lincoln, Neb.

424 Dewey Avenue.

APPEARANCE OF OSSIFICATION CENTERS

GROUPINGS OBTAINED FROM FACTOR ANALYSIS

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The appearance of ossification centers roughly follows a standard time schedule. But irregularities in the time and order of appearance of centers are common enough to make assessment of "skeletal age" by the Todd [1] or Flory [2] atlases in many cases difficult if not impossible.

It was felt that these variations could be better understood if one could demonstrate that there are groups of ossification centers and that it is these groups which show more or less independence in their times of appearance. For instance, if one center of a certain group were retarded, all other centers of that group should also tend to be retarded. Do such groups exist? This can best be answered statistically. A "group" implies mutual relations among variables. It was therefore decided to intercorrelate the ages at which the ossification centers appear.

A group of apparently normal, healthy white children is being observed at the Samuel S. Fels Research Institute. Part of this study consists of periodic roentgen examinations of the skeleton. Roentgenograms of the upper and lower extremities are taken at birth, at the age of 1, 3, 6, 9 and 12 months, and every six months thereafter. The times of appearance of the ossification centers are estimated to the closest month.[3] Mean times of appearance and standard deviations for all centers of the extremities appearing up to 8 years have been calculated.[4]

It was necessary to limit the analysis to a relatively small group of variables. The total number of centers appearing between birth and 8 years is approximately sixty. Intercorrelation of sixty variables would require the cumbersome calculation of seventeen hundred and seventy coefficients. By selecting nineteen centers the work was reduced to the

From the Samuel S. Fels Research Institute, Antioch College.

1. Todd, T. W.: Atlas of Skeletal Development, St. Louis, C. V. Mosby Company, 1937.

2. Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monographs of the Society for Research in Child Development, Washington, D. C., National Research Council, 1936, vol. 1, no. 3.

3. These estimates have been made for several years by Miss Idell Pyle of this institute. Intimate knowledge of the early stages of the centers makes it possible to obtain reliable estimates.

4. Pyle, I., and Sontag, L. W.: Variability in Onset of Ossification in Epiphyses and Short Bones of Extremities, to be published.

computation of one hundred and seventy-one correlation coefficients. These centers were selected for the following reasons:

1. They represent a variety of types: the upper and lower extremities, centers appearing early and late, centers highly variable or fairly constant in the times of appearance, round bone centers, epiphyses of long and short bones and one sesamoid bone (the patella).

2. The selection eliminates those centers which may be present at birth (for which times of appearance could not be calculated) and all inconstant ones (some of the middle and distal phalangeal epiphyses of the toes).

TABLE 1.—*Mean Ages in Months (M) at Which Centers Appear and Coefficients of Variability* ($CV = \frac{100.\sigma}{M}$)

	Girls		Boys	
	M	CV	M	CV
Head of femur	4	41	4	46
Capitellum	4	52	5	63
Distal epiphysis of fibula	9	27	12	39
Distal epiphysis of radius	11	38	13	37
Medial cuneiform	17	48	21	29
First metacarpal	20	25	30	24
Proximal phalanx of first toe	21	22	30	17
Middle cuneiform	21	37	28	40
Triquetral	22	56	28	52
First metatarsal	21	17	28	18
Proximal phalanx of first finger	22	27	34	23
Navicular (foot)	25	43	34	39
Lunate	32	55	46	43
Patella	35	25	52	22
Navicular (hand)	47	32	60	23
Greater multangular	48	25	64	31
Proximal epiphysis of radius	48	26	63	27
Distal epiphysis of ulna	63	24	82	13

Thirty-one children (12 boys and 19 girls) had all nineteen centers. The ages at which these centers appeared were intercorrelated.[5] Inspection of table 2 shows correlations ranging from 0 to 0.85. There were no significant negative correlations, which is not surprising. (A negative correlation would mean that acceleration in the appearance of one center would be associated with retardation in the appearance of another one.)

The correlations have been subjected to factor analysis. This is a mathematical method which isolates the properties shared by a group of

5. Objections may be raised to combining the data on boys and girls, since girls are considerably advanced over boys in the appearance of ossification centers. However, they differ only in the rate of development, not in the sequence of appearance of the centers. The ratio of the mean appearance time for boys to the mean appearance time for girls is practically identical for all centers. For purposes of this study girls may be considered simply as physiologically advanced boys.

TABLE 2.—*Intercorrelations of Appearance Times of Ossification Centers* *

First factor loadings	0.85	0.81	0.79	0.77	0.68	0.59	0.51	0.16	0.05	0.26	—0.01	0.13	0.06	0.35	0.37	0.04	0.01	0.31	0.04
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.
1. Navicular of foot																			
2. Triquetral	0.64																		
3. Middle cuneiform	0.74	0.68																	
4. Lunate	0.65	0.62	0.53																
5. Navicular of hand	0.62	0.36	0.65	0.56															
6. Greater multangular	0.49	0.38	0.61	0.50	0.76														
7. Medial cuneiform	0.59	0.58	0.63	0.59	0.56	0.43													
8. Head of femur	0.25	0.44	0.07	0.37	0.26	0.36	0.28												
9. Distal epiphysis of radius	0.16	0.26	0.19	0.16	0.48	0.43	0.46	0.38											
10. First metacarpal	0.39	0.29	0.56	0.46	0.63	0.68	0.43	0.27	0.37										
11. Distal ulna	0.22	0.08	0.25	0.19	0.59	0.61	0.08	0.18	0.32	0.58									
12. First metatarsal	0.31	0.18	0.45	0.34	0.65	0.55	0.42	0.18	0.37	0.84	0.57								
13. Patella	0.15	0.04	0.30	0.15	0.58	0.61	0.27	0.26	0.38	0.59	0.58	0.54							
14. Capitellum	—0.01	0.25	0.22	0.19	0.30	0.37	0.39	0.44	0.54	0.41	0.29	0.37	0.25						
15. Proximal epiphysis of fibula	0.24	0.41	0.39	0.25	0.47	0.52	0.35	0.36	0.59	0.53	0.47	0.41	0.51	0.47					
16. Proximal phalanx of first finger	0.12	0.18	0.34	0.19	0.52	0.58	0.30	0.17	0.46	0.66	0.06	0.65	0.77	0.41	0.50				
17. Proximal phalanx of first toe	0.15	0.15	0.25	0.32	0.51	0.51	0.25	0.23	0.37	0.74	0.70	0.85	0.61	0.39	0.49	0.59			
18. Distal epiphysis of fibula	0.18	0.20	0.31	0.06	0.43	0.48	0.50	0.47	0.72	0.42	0.34	0.42	0.52	0.72	0.64	0.46	0.38		
19. Proximal epiphysis of radius	00	0.11	0.11	0.03	0.45	0.52	0.11	0.27	0.50	0.49	0.55	0.47	0.55	0.46	0.62	0.59	0.55	0.56	
Second factor loadings	— 04	04	17	03	52	56	14	20	48	59	59	61	65	65	69	70	72	72	76

* The variables are arranged in a manner that makes two groups evident. High correlations (within each group) are found in the squares at the upper left and the lower right. The groups are mutually exclusive except for variables 5 and 6, which are related to both groups (rectangle at center of lower part of table).

TABLE 3.—*Factor Loadings*

General Factor		Epiphysis Factor			Round Bone Factor			Third Factor	
			Method			Method			
			Centroid	Bifactor		Centroid	Bifactor		Centroid Method
Distal epiphysis of fibula	0.663	Proximal epiphysis of radius	0.768	0.690	Navicular (foot)	0.852	0.809	Distal epiphysis of radius	0.620
Proximal epiphysis of fibula	0.641	Distal epiphysis of fibula	0.722	0.333	Triquetral	0.811	0.477	First metacarpal	0.610
Distal epiphysis of radius	0.636	Proximal phalanx of first toe	0.719	0.781	Middle cuneiform	0.788	0.907	First metatarsal	0.595
Greater multangular	0.621	Proximal phalanx of first finger	0.695	0.606	Lunate	0.769	0.582	Head of femur	0.540
Capitellum	0.613	Proximal epiphysis of fibula	0.686	0.370	Navicular (hand)	0.684	0.437	Distal epiphysis of ulna	0.524
First metacarpal	0.557	Capitellum	0.653	0.206	Greater multangular	0.587	0.269	Proximal phalanx of first finger	0.499
Medial cuneiform	0.555	Patella	0.649	0.687	Medial cuneiform	0.571	0.523	Medial cuneiform	0.489
Triquetral	0.544	First metatarsal	0.607	0.676	Proximal epiphysis of fibula	0.367		Patella	0.431
Head of femur	0.536	Distal epiphysis of ulna	0.594	0.708	Capitellum	0.350		Proximal phalanx of first toe	0.425
Lunate	0.516	First metacarpal	0.586	0.615	Distal epiphysis of fibula	0.310		Lunate	0.221
Navicular (hand)	0.516	Greater multangular	0.558	0.478	First metacarpal	0.255		Greater multangular	0.201
First metatarsal	0.414	Navicular (hand)	0.519	0.519	Head of femur	0.157		Navicular (foot)	0.192
Navicular (foot)	0.389	Distal epiphysis of radius	0.484	0.238	First metatarsal	0.128		Middle cuneiform	0.190
Proximal phalanx of first finger	0.387	Head of femur	0.199		Patella	0.055		Navicular (hand)	0.147
Patella	0.345	Middle cuneiform	0.168	0.459	Distal epiphysis of radius	0.046		Proximal epiphysis of radius	0.096
Proximal phalanx of first toe	0.318	Medial cuneiform	0.140		Proximal phalanx of first toe	0.044		Triquetral	0.088
Distal epiphysis of ulna	0.276	Triquetral	0.042		Proximal epiphysis of radius	0.036		Proximal epiphysis of fibula	0.040
Proximal epiphysis of radius	0.268	Lunate	0.025		Proximal phalanx of first finger	0.012		Distal epiphysis of fibula	−0.010
Middle cuneiform	0.177	Navicular (foot)	−0.038		Distal epiphysis of ulna	−0.010		Capitellum	−0.200

variables, i. e., the qualities which make for the high intercorrelations. These are the "factors." Three such factors were found (see appendix). In order to minimize technical discussion the variables in the correlation table are arranged in such a manner as to make two of the factors evident on inspection. It may be seen that the high coefficients of correlation are found in two areas, the square in the upper left and the square in the lower right portion of the table, while the low and insignificant coefficients are found at the lower left.

The question raised in the first paragraph can now be answered: There are at least two groups of variables. In each group the variables (the times of appearance of the centers) are closely related to each other but are related hardly at all to the variables of the other group. This means that all centers of a group will tend to be relatively retarded (or advanced) if one center of the group is retarded (or advanced). It does not mean that the centers appear at approximately the same age.

Let us now examine the groups. Variables 1 to 7 are the times of appearance of the centers of the round bones (carpals and tarsals). "Round bone factor" seemed an appropriate name for the properties shared by them. Variables 9 to 19 are for epiphyses and the patella. Their common qualities were called the "epiphysis factor." It will be seen that the head of the femur (variable 8) has not much in common with either group, while two other variables, those for the navicular bone of the hand (5) and the greater multangular (6) are related to both groups. In technical terms variables 5 and 6 have large "loadings" on both factors. It is interesting that the patella, a sesamoid bone, groups itself with the epiphyses.

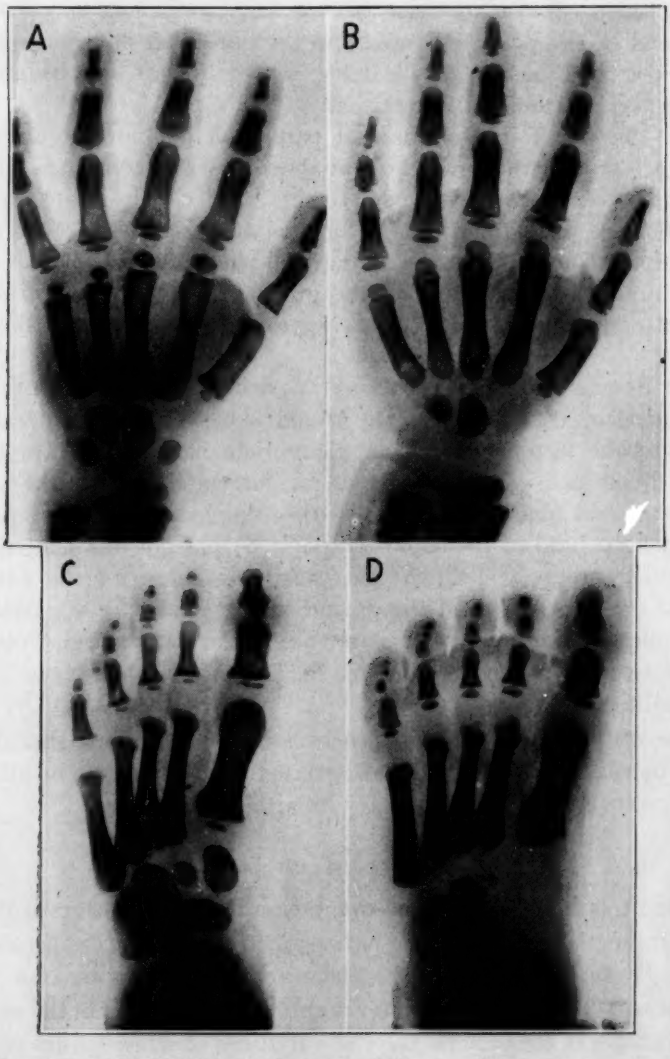
The mathematical analysis also isolated a third factor shared by a group of variables which seem to have nothing physiologic or anatomic in common. This factor is possibly an artefact.

COMMENT

Almost as interesting as the emergence of the two factors is the fact that certain other groupings did not appear. There is no "upper extremity" or "lower extremity" factor and there is no indication of a "time" or "maturity" factor. The groups are entirely independent of the sequence of appearance of the centers. Not all variations or irregularities of center appearance can be explained by these factors. But the findings strongly argue against the postulates of Francis and Werle [6] that intercurrent illnesses are the major cause of variation in the sequence of appearance of the centers.

6. Francis, C. C., and Werle, P. P.: The Appearance of Ossification Centers from Birth to Five Years, Am. J. Phys. Anthropol. **24**:273, 1939.

It seems reasonable to assume that the remaining centers of round bones and epiphyses (not included in this study) will fall into the same two groups. If so, one may expect to find cases in which the carpals



In *A* and *C* (child M. M.) development of the carpal and tarsal centers is considerably advanced over development of the epiphyses. In *B* and *D* (child T. S.) development of the epiphysial centers is advanced over development of the carpals and tarsals.

and tarsals appear early while the epiphyses (and the patella) appear late and vice versa. Such cases actually occur. The difference between

these types can be seen in the hands and feet (fig. 1); it is observable not only in the appearance of the centers but in their relative maturation. The two types can be well distinguished at a stage at which all centers are present.

The skeletal age of such "atypical" children cannot be assessed by the methods of Todd [1] or Flory,[2] but it is possible to assign these children a skeletal age from the total number of ossification centers.[7] This method, while useful in the average case, is of less value in these atypical cases, since it arbitrarily weighs all centers equally. The number of epiphyses is much larger than the number of round bones. Epiphysial advancement or retardation would influence the skeletal age rating correspondingly more than changes in round bone development.

The problem may be solved in one of two ways:

1. By the establishment of an atlas with three standards for each age group: one with epiphysial development advanced over round bone development; one with round bone development advanced over epiphysial development, and a third standard for persons in whom both groups of centers are equally developed (the present type of standard).

2. By the establishment of two skeletal ages: the round bone skeletal age and the epiphysis skeletal age. This is the more logical method. It could be done either by the use of the conventional atlas standards or by counting separately the round bone and the epiphysial centers.

Among this group of children acceleration of development of the round bones is often associated with general acceleration in skeletal development, and retardation of development of the round bones, with general retardation in skeletal development. The latter was found in all 4 children (2 boys and 2 girls) of one family. This introduces two other problems:

1. Could these two factors have a genetic meaning? Are they mendelian characters? Or

2. Could these factors respond differently to endocrine influences or any other disturbance of growth? For instance, does hypothyroidism cause a more severe retardation of development of round bones than of epiphyses?

The material is not adequate to afford an answer to these questions. They have been mentioned here in order to stimulate further research and to illustrate the potential usefulness of factor analysis in biologic and medical research.

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7. Sontag, L. W.; Snell, D., and Anderson, M.: Rate of Appearance of Ossification Centers from Birth to the Age of Five Years, Am. J. Dis. Child. **58**:949 (Nov.) 1939.

SUMMARY

The ages were determined at which certain centers of ossification appeared in a group of 31 children. These data were intercorrelated and subjected to factor analysis.

The analysis yielded three factors, a "round bone" factor, an "epiphysis" factor and a third factor which had no obvious meaning (possibly an artefact).

An appreciation of the first two factors helps one to understand certain cases in which skeletal development is atypical. Methods are suggested by which meaningful "skeletal ages" may be assigned in such cases.

Various possible applications of these observations are outlined.

APPENDIX: STATISTICAL TECHNIC

I have closely followed the method for centroid factor analysis outlined by Guilford.[8] The ranked factor loadings are given in table 3.

It was thought that some people might object to the use of the centroid method, claiming that the method forced the data into a two factor pattern, neglecting a single general factor. For this reason Holzinger's bifactor method[9] was used on the same data. The analysis yielded a general and two group factors (table 3). It is easily seen that the group factors correspond closely to the "epiphysis" and the "round bone" factor of the centroid method. No third group factor could be found, though there were a few fairly large residual correlations left. This confirms the previous suspicion that the third factor isolated by the centroid method was an artefact.

The general factor contributes 24 per cent to the total variance, while the two group factors combined contribute 36 per cent. This can now be interpreted as follows: There is still some justification for considering skeletal age (based on the appearance of ossification centers) as a single unit. On the other hand, the two factor pattern is a better expression of the relationships, and the concept of two skeletal ages (as defined) is not only sound but superior to the old unitary concept.

I have received much valuable advice on the statistical analysis from Dr. T. W. Richards of this institute. Miss M. J. Pobst and Miss J. Lipford did most of the calculations.

Samuel S. Fels Research Institute.

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OPTIMAL REACTION FOR STARCH-LIQUEFYING ACTIVITY OF DUODENAL AMYLASE OF INFANTS

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There is an optimal hydrogen ion concentration for the activity of each enzyme, and there are also upper and lower limits of reaction above or below which the enzyme is inactive or is destroyed.[1] Enzymes of different origins, even though they act on the same substrate, vary in the hydrogen ion concentration at which they exert their greatest activity.[2] In addition to the origin of the enzyme, the optimal reaction is affected by the type of buffer solution,[3] the nature of the substrate,[4]

From the Department of Pediatrics of the Johns Hopkins and of Duke University.

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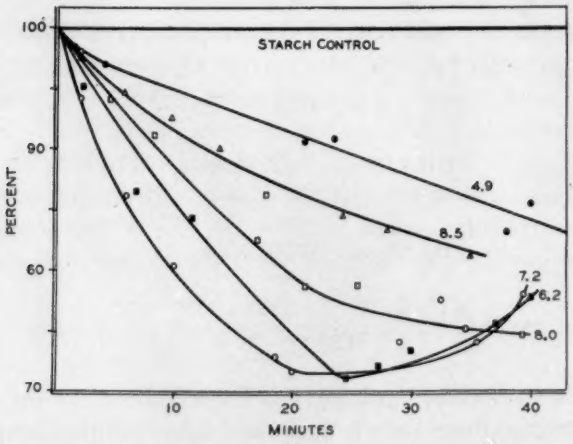

Chart 1.—Activity of duodenal amylase at p_H 4.9 to 8.5. One-tenth cubic centimeter of duodenal contents, diluted 1:4 with saline solution, was added to 10 cc. of 6 per cent starch suspension buffered with twentieth-molar phosphate solution, and the amylase activity was determined viscometrically at 34 C.[8]

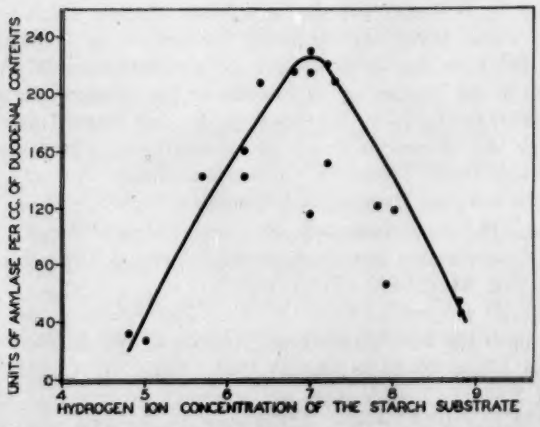

Chart 2.—Activity of duodenal amylase at p_H 4.8 to 8.6. One-tenth cubic centimeter of duodenal contents from patient 1 was added to 10 cc. of 4 to 6 per cent starch suspension buffered with twentieth-molar phosphate solution, and the amylase activity was determined viscometrically at 34 C.[8]

the degree of purification of the enzyme,[4] the method of measurement [5] and the temperature at which the enzymic activity was studied.[6] These differences in the optimal reactions of the same enzyme may be fictitious and be caused by the difficulty of measuring accurately the reaction of different buffers, or they may be due to the stimulating or inhibiting action of the salts comprising the buffers or of the end products of the enzymic reaction which may combine with the salts of the buffer.[7] For example, the optimal hydrogen ion concentration of pancreatic amylase was found to be 7, of malt amylase 4.45 and of Aspergillus oryzae (taka diastase) 4.8 when the copper reduction method [2] was used. With the viscometric method of measurement [8] with unbuffered starch, the optimal

TABLE 1.—*Comparison of the Activity of the Amylase of the Duodenal Contents of Infants at Different Hydrogen Ion Concentration*

Starch Concentration	Relative Amylase Activity at				
	1	2	3	4	5
0% *	p_H 7.2	6.2	8.0	8.5	4.9 (fig. 1)
4% *	p_H 6.8	7.3	6.2	5.7	8.0
6% *	p_H 7.2	6.2	8.0	8.9	5.0
2% †	p_H 6.2	8.4	7.1	5.3	
2% †	p_H 6.9	6.0	7.7	5.2	8.0
2% †	p_H 6.9	6.0	5.2	7.7	7.9
2% †	p_H 6.9	7.9	5.0	6.0	7.7
2% †	p_H 8.0	7.0	9.0	6.0	5.0
2% †	p_H 8.0	7.0	6.0	9.0	5.0
Mean	p_H 6.9				

* Patient 1, H. L. H., 18 months of age, had normal digestion but had had diarrhea during the previous summer. The duodenal contents were collected and kept in a refrigerator. The amylase activity was determined viscometrically at 34 C. by adding 0.1 cc. of duodenal contents diluted 1:4 with saline solution to 10 cc. of starch suspension in twentieth-molar phosphate buffer solution at p_H 3.0 to 9.0.

† Patient 2, H. L. H., 30 months of age, had normal digestion but had had diarrhea during the previous summer. The duodenal contents were collected and kept in a refrigerator. The amylase activity was determined viscometrically at 34 C. by adding 0.1 cc. of duodenal contents diluted 1:8 with tenth-molar phosphate buffer at p_H 7.0 to 10 cc. of starch suspension in twentieth-molar phosphate buffer solution at p_H 3.0 to 9.0.

reaction for the amylase of Aspergillus oryzae (taka diastase) was p_H 3.0, but with starch buffered with half-normal universal buffer it was p_H 4.0.[3]

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In order to determine the optimal hydrogen ion concentration of the amylase of the duodenal contents of infants, the activity of thirteen specimens of duodenal contents collected from 2 infants was determined viscometrically at 34 C. using as substrates 2 to 6 per cent Lintner soluble starch suspended in twentieth-molar solution of sodium and potassium phosphate at hydrogen ion concentrations of 4.9 to 9.0. Reactions of p_H 3.0 to 9.0 had little effect on the viscosity of the starch suspensions, but partial precipitation occurred at p_H 1 and 2. The methods are described elsewhere.[8]

The results of each titration were plotted (chart 1) and the number of units of amylase per cubic centimeter calculated. The hydrogen ion concentration at which the greatest activity occurred was designated as 1, the next highest as 2, etc. As may be seen from the results of forty-four titrations at reactions from p_H 4.9 to 9.0 tabulated in table 1, the greatest activity of the various specimens was between p_H 6.2 and 8.0 with a mean of p_H 6.9.

This optimal reaction also is illustrated in chart 2, in which are recorded the results of eighteen titrations of the duodenal contents of patient 1 at hydrogen ion concentrations of 4.8 to 8.6. The irregularities of chart 2 probably are due to the fact that the specimen of duodenal contents had been kept in a refrigerator for six weeks and that the titrations were made over a period of twenty-two days with concentrations of 4 to 6 per cent starch.

CONCLUSION

The optimal reaction of the amylase of the duodenal contents of infants is p_H 6.9 to 7.0, when determined viscometrically with starch suspensions in twentieth-molar phosphate buffer solutions.

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ORAL PROPHYLAXIS FOR POISON IVY DERMATITIS IN CHILDREN

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In spite of the widespread use of various types of specific prophylactic measures for poison ivy dermatitis, the true value of such treatment still must be proved.[1] The problem is especially important for children, because of the frequency of this form of dermatitis among them and the ease of extensive secondary infection when the dermatitis occurs.

This report is concerned only with the analysis of the value of the oleoresin extract of poison ivy as a specific prophylactic agent when given by mouth. Chemical prophylactic materials for local use on the skin, such as soap coverings and oxidizing compounds,[2] have not been found to be effective for appreciable lengths of time.[3] Methods have been suggested for hyposensitizing the skin by local applications of diluted poison ivy antigen, but little work has been done on this subject.[4] Of course, the oldest form of specific prophylaxis was the chewing of the leaves of the plant. It is said that some of the American Indians used that method. Alderson [5] reported that fatalities resulted occasionally among the California Indians and Mexicans from the eating of leaves of poison oak, the toxic substance of which is very closely related to that of poison ivy, if not actually the same. In some rural communities one still hears that farmers claim the chewing of this ivy leaf is a valuable preventive aid. Although Schamberg [5] popu-

Extract furnished by Lederle Laboratories, Inc., Pearl River, N. Y.

* Member of the Committee for the Cooperative Clinical Study of Poison Ivy Desensitization.

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larized an antigen for oral administration, extracts had been used in 1912 by Attix [6] and later by French,[5] Duncan,[5] Strickler [5] and Spain and Cooke.[7] Soon the intramuscular administration of an extract of poison ivy became more popular.

Interest in the oral method of prophylaxis has been revived recently through the brilliant work of Shelmire since 1938. In simple but detailed clinical experiments he has demonstrated remarkable progress in all clinical phases of poison ivy dermatitis. He first obtained a potent ether extract from poison ivy and proved that this extract was still potent after five years. Corn oil was used as the vehicle for this oleoresin. With this mixture he was able to establish and prove protection against poison ivy in a group of 20 persons.[8] In this group there were 3 children under 14 years of age. Other recent surveys of the value of oral prophylaxis have been made by Zisserman,[9] who used enteric-coated tablets of very small dose for 100 patients and reported no good results, and by Gold and Masucci,[10] who used poison ivy tablets containing the poison ivy oleoresin of much higher dose and reported success. In 1927 Spain and Cooke [7] described a poison ivy tablet which had produced favorable results. For some years I used a tincture administered by mouth with very little, if any, effect, and recently I have used capsules containing unstandardized amounts of dried poison ivy extracts, also with poor results.

Those who favor the oral method of administration believe that the reported failures from intramuscular injections have been due to the fact that too small amounts of antigen were used. Shelmire [8] has claimed that the "ingestion of approximately 2 cc. of a stable and potent ivy leaf oil is necessary to reduce the cutaneous sensitivity of the average person from clinical to subclinical level." If this arbitrary amount is correct, intramuscular injections would have to be continued for very long periods. When large amounts are administered by this method, the local reactions are severe. So, until the extract from poison ivy is better refined chemically and manufacturers can concentrate it more (or even synthesize it), the oral method of administration is to be preferred in order to secure adequate dosage. When

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the oral method is used, one must be certain that the extract is potent and that it is given for a sufficient time. Since Zisserman [9] in his series of cases reported no reactions from his enteric-coated tablets containing 0.01 mg. of ether-soluble plant extract, it is doubtful whether enough antigen was absorbed (or was even present in the tablets) to reduce the cutaneous sensitivity to an appreciable degree. No cutaneous tests were done to prove this. Zisserman [9] himself considered that the dosage might have been inadequate.

Some of the discrepancies in the reports of the value of poison ivy antigen may have been due also to the lack of standardization of the extracts. Sharlit [11] has indicated that there is no definite method of titrating the strength of extracts made from chance samples of leaves. Furthermore, he has claimed that there has been as much as 300 per cent variation in the strength of extracts made from different batches of leaves. Work is being done at present to find a method to standardize extracts in terms of "dermatitis-producing units." Bailey [12] has devised a method of chemical standardization that is reported to be accurate within a range of 5 per cent. Shelmire [8] stated that "any oleoresin employed for oral therapy must cause a positive reaction on the back of a person of average sensitivity when diluted at least 2,500 times with corn oil and applied in a patch test." The one extract used in this report (an acetone extract in corn oil diluted 1:25) fulfilled this requirement.

The subjects included in this study were children who had a history of repeated episodes of poison ivy dermatitis. Thirty-nine children were selected. Ten of the patients in previous years had had other types of prophylactic treatment, and these procedures had failed to give protection to 8 patients. Three of the children were in the midst of an actual episode of poison ivy dermatitis when the antigen was given. All the other children in the series were given patch tests with varying dilutions of the antigen to determine their index of cutaneous sensitivity before the medication was started. Thirteen children had this cutaneous test repeated after use of the antigen was stopped (see table). The children were seen again in the late fall to determine, among other things, the incidence of poison ivy dermatitis. It is important to note that the degree of exposure to the plant was uncontrolled and the history alone was used to determine this degree of exposure and of protection. There were no "field tests" in this study.

The children were observed in private practice and in a special poison ivy clinic at the Children's Hospital. The ages varied from 3 to 15 years, with the average age about 10. The records are complete

11. Sharlit, H.: Personal communication to the author.
12. Bailey, C.: Personal communication from A. F. Coca.

for only 36 of the 39 patients. Only the initial amount of treatment is known for the 3 missing patients. It has been reported also that these 3 patients did not get poison ivy dermatitis during the period of observation. Twenty-four of these 39 patients had cutaneous tests prior to taking the antigen. The dilutions of antigen preparation in corn oil for patch tests were 1:5,000, 1:1,000 and 1:500. Only 4 patients did not react to the 1:500 dilution. On 2 of these patients no additional concentrations were used. The other 2, however, failed to react to 1:50 and 1:25 dilutions after ingestion of the antigen. These less sensitive patients were not considered then for analysis of changes in cutaneous sensitivity. The total dose received by all the children varied from 2 drops to 25 cc. Fourteen children took 20 cc., and 13

Change in Cutaneous Sensitivity of Thirteen Children Tested Before and After Oral Administration of Antigen

Children	Total Dose, Cc.	Reaction Before Treatment			Reaction After Treatment			Reactions Due to Treatment
		1:500	1:1,000	1:5,000	1:500	1:1,000	1:5,000	
1	12	+	+	0	0	0	0*	0
2	20	+	+	+	0	0	0	Focal reaction
3	20	+	+	0	0	0	0	0
4	25	+	+	0	0	0	0*	0
5	20	+	+	+	0	0	0	Generalized pruritus
6	15	+	+	0	0	0	0	Papular dermatitis
7	20	+	+	+	0	0	0	0
8	20	+	+	0	0	0	0	Pompholyx-like eruptions
9	10	+	+	0	0	0	0	0
10	30 drops	+	+	+	+	0	0	Pruritus ani
11	20	+	+	0	0	0	0	Focal flare up
12	20	+	0	0	0	0	0*	0
13	20	+	0	0	0	0	0*	0

* Post-treatment tests elicited negative responses also to dilutions of 1:25, 1:50 and 1:100.

children took less than 10 cc. The reason for the smaller doses was voluntary discontinuance of treatment by the patients when reactions occurred.

The patch tests before treatment were begun in April 1941 and tests after treatment in June 1941. Thirteen of the 20 patients who reacted positively had post-treatment tests. Eleven of these 13 showed definite improvement in reactions to the patch tests; all of these 11 patients were now immune to a 1:500 dilution of the extract and even to a 1:25 dilution. One of the patients who failed to show any appreciable decrease in cutaneous sensitivity had received a total dose of 12 cc. of antigen. This patient also proved her lack of protection by acquiring a poison ivy dermatitis, which was milder, however, than in previous years. Prophylactic treatment had never been given to her previously. The other patient who failed to show changes in

cutaneous sensitivity had had only 10 drops of the antigen. The majority of the patients who showed improvement in the reactions to the post-treatment test had had more than 10 cc. of antigen.

Check-up examination in the fall revealed that only 4 of this entire group of 39 patients had had poison ivy dermatitis during the period of observation. As already noted, the patient's histories were the chief means of determining this. Only 1 of these patients in whom the prophylaxis failed was seen in the clinic and the diagnosis established. Another of the patients who had poison ivy dermatitis in October had received 10 cc. of the antigen and stopped taking it in July. At that time post-treatment cutaneous tests had indicated improvement. Another child of this group had taken only 5 drops and another about 10. Pretreatment cutaneous tests of these patients had indicated a high degree of sensitivity, but post-treatment tests were not made.

Three children were given this antigen during the actual course of poison ivy dermatitis. There were no reactions to the antigen, nor was the course of the dermatitis changed. Similar results were noted also in the case of 2 adults who took the antigen during an episode of poison ivy dermatitis. This is contrary to the experience of Shelmire,[13] who has found that such treatment exaggerates the eruption.

One of the interesting phases of this work was the study of the reactions to the ingestion of this antigen in corn oil. In the early days of therapy by poison ivy antigens, there were reports of dermatitis caused by spilling the antigen on the skin, of pruritus ani and of urticaria.[14] However, most of these reactions were not severe, probably because the antigen in most instances was so weak. The reactions were more pronounced, however, when the antigen was used as a therapeutic agent. Shelmire [15] has described briefly the diverse cutaneous reactions to his antigen in the form of "flare-up of skin and mucous membrane patch sites healed six months to two years, dermographism, pruritus ani without visible perianal dermatitis, pompholyx-like eruption of the hands, mild diarrhea and widespread erythematous and urticarial eruptions." He has also described a focal flare-up following the use of his antigen in an area which had been healed for ten years. Only 1 of his patients showed toxic manifestations on more than one occasion. There were no apparent visceral reactions.

In their recent series of 20 patients Gold and Masucci [10] observed reactions in all but 4. Their antigen was poison ivy oleoresin in a tablet. They believed the tablet was safer for children, because there was less danger of spilling the oleoresin on the skin.

13. Shelmire, B.: Personal communication to the author.

14. Goldman, L.: The Reactions Following the Therapeutic Use of Poison Ivy Antigen for Poison Ivy Dermatitis, J. Med. **20**:294 (Sept.) 1939.

15. Shelmire, B.: Contact Dermatitis from Vegetation, South. M. J. **33**:337 (April) 1940.

Of the group of 39 patients in my report, 18 took as an initial dose 3 drops a day. This was 2 drops more than the dose recommended for this corn oil antigen. Sixteen (89 per cent) had reactions within twenty-four hours after the ingestion of 3 to 6 drops; 6 of these had a generalized morbilliform dermatitis; 4 had an extensive papulovesicular dermatitis resembling an actual poison ivy dermatitis of moderate degree; 4 had a severe pompholyx-like eruption only on the hands; 3 had generalized pruritus without cutaneous lesions, and 1 had pruritus ani. Four children had focal flare-up reactions consisting of a papulovesicular dermatitis limited to a site severely involved the previous summer. In an adult group 4 of the 5 patients given a similar dose had reactions. However, 1 child was able to take 4 drops daily as an initial dose without reactions. Practically every patient who started on 3 drops a day and had reactions continued on the dose of a drop every day and gradually increased this every other day.

Twenty-one other children were then given 1 drop every other day. Of the latter group only 6 had reactions: 1 a focal flare-up, 1 a generalized papular dermatitis, 1 a pompholyx-like dermatitis on the hands, 1 a generalized pruritus and 2 pruritus ani without dermatitis. The dose in all groups was then increased by 1 drop until 10 to 15 drops was taken daily. The antigen was continued for two months or even longer. Of these 22 patients with reactions, only 1 had another reaction later in the course of therapy when use of the drops was resumed. These reactions to this antigen were therefore evidences of overdoses. The fact that an antigen can provoke reactions in the person of average sensitivity indicates that it is a potent antigen. Moreover, as Spain and Cooke [7] reported previously, such reactions signify that epidermal contact is not the only way to acquire poison ivy dermatitis. It is suggested, although not proved, that at times, even with inadequate total dosage, cutaneous reactions to the antigen may be of some protective value.

The antigen was dispensed in a dropper bottle together with a supply of no. 1 gelatin capsules. The patients were instructed to fill a capsule with the dose indicated and take it at the close of a meal. Older children filled their own capsules. The mothers of younger children were instructed in the technic and given the schedule of doses. No accidents were reported in this series.

SUMMARY AND CONCLUSIONS

By the use of Shelmire's antigen and technic there has been definite progress in producing a specific prophylaxis against poison ivy dermatitis.

A similar antigen administered orally was used as a prophylactic agent for 39 children with a history of repeated episodes of poison ivy dermatitis. Thirteen patients had quantitative tests for cutaneous sensitivity to poison ivy before and after treatment, and 11 of these children showed definite improvement in cutaneous sensitivity after ingestion of the antigen.

Eighty-nine per cent of the patients had reactions to the extract when the initial dose was 3 drops a day, and 28 per cent had reactions when the initial dose was started as 1 drop every other day. There were no visceral reactions in this series.

Suggestive evidence of a decrease in cutaneous sensitivity to poison ivy was the fact that only 4 patients in the entire series acquired poison ivy dermatitis from presumed ordinary exposure. No special controlled field contact tests were done.

As a method of providing adequate doses of antigen these new potent oral antigens with their prolonged schedule of dosage are advised. Whenever possible, quantitative tests of cutaneous sensitivity should be done before and after treatment in order to follow the patients more critically. More controlled exposure tests should be done before these antigens are advised for routine, uncontrolled use.

In view of the long duration of the oral prophylactic treatment it is evident that this treatment should be initiated by the middle of March if possible.

Follow-up studies in many of the patients were made possible chiefly through the efforts of Mrs. Bertha Bahlman, head of Social Service Department of the Children's Hospital.

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ISOLATION OF INTESTINAL PATHOGENS FROM PRESERVED STOOLS OF CHILDREN

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The isolation of dysentery bacilli from the stools of children with clinical dysentery or diarrhea has been investigated from several viewpoints. Some authors have been concerned with the elaboration of new methods or mediums, and others, with the separation of the etiologic agents into groups and subgroups.

Almost all investigators have noted that the organisms are extremely difficult to isolate in a large percentage of cases, that they die in the stools shortly after passage and that many patients who have clinical dysentery, with mucus and blood in the stools, never have positive cultures. Blacklock and Guthrie [1] noted, for example, that it became harder to isolate the dysentery bacilli after the acute stages of the disease had passed, but they had been able to obtain a few positive cultures from the intestinal scrapings taken at autopsy. Carter [2] noted that positive cultures were obtained from 50 per cent of diarrheal liquid stools examined, 13 per cent of diarrheal stools with mucus and only 3 per cent of soft diarrheal stools.

Blatt and Shaw [3] demonstrated clearly the unreliability of cultures for dysentery bacilli by sending stools from persons proved to have the disease to three different laboratories. One laboratory obtained positive cultures from 51 per cent, another from 25 per cent and the authors themselves from 44 per cent. They noted, however, that the organisms remained alive in mucus which was stored for one year.

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The clinical material was supplied by direction of M. L. Blatt, M.D., and under the supervision of Irma McFadden, M.D., from the Children's Division of the Cook County Hospital.

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2. Carter, H. S.: Dysentery in the Glasgow Area, J. Path. & Bact. **45**:447, 1937.

3. Blatt, M. L., and Shaw, N. G.: Bacillary Dysentery in Children: A Study of Three Hundred and Fifty-Six Cases from the Children's Division in the Cook County Hospital, Chicago, Arch. Path. **26**:216 (July) 1938.

Garrison and Mayfield [4] obtained positive cultures from 33 per cent of stools sent to the laboratory as soon as possible for culture. In a recent outbreak of Shiga dysentery which occurred in Michigan, Block and Ferguson [5] reported that isolations in the central state laboratory gave such poor results that field laboratories were established. In these field laboratories half of the stools were put into 30 per cent glycerin and sent to the central laboratory, while the other half were cultured immediately. Ten stools which yielded the organisms when cultured immediately proved sterile when cultured twenty-four hours later in the central laboratory. It was discovered that the dysentery organisms survived only two hours and that in most cases they could be isolated only when examination was made within one hour.

Several investigators have been interested in the preservation of specimens, in the hope that more positive results could be obtained. One of the earliest and most useful reports was that of Dudgeon and associates,[6] who showed that dysentery bacilli did not survive in acid stools but that the addition of 1.5 per cent of normal sodium hydroxide solution maintained the stools in an alkaline state and kept the organisms alive.

Teague and Clurman [7] suggested 30 per cent glycerin in a 0.6 per cent sodium chloride solution as a preservative for typhoid bacilli. This preservative has been in general use for fecal specimens since 1916. Recently Bangxang and Eliot [8] investigated the use of sodium citrate–sodium desoxycholate in different concentrations, 30 per cent neutral glycerin, 30 per cent Merck reagent glycerin and lithium chloride glycerin as preservatives, both in pure cultures of dysentery bacilli and in cultures added to feces. The citrate-desoxycholate preservatives proved superior to the glycerin solutions. The authors also suggested mandelic acid in various concentrations as a preservative worthy of further investigation.

It is interesting to note that the average p_H of these various preservatives ran as follows: The 30 per cent neutral glycerin showed a p_H of

4. Garrison, N. F., and Mayfield, C.: A Clinical and Bacteriological Survey of Bacillary Dysentery, Mississippi Doctor **16**:50, 1939.

5. Block, N. B., and Ferguson, W.: An Outbreak of Shiga Dysentery in Michigan 1938, Am. J. Pub. Health **30**:43, 1940.

6. Dudgeon, L. S.: Studies of Bacillary Dysentery Occurring in the British Forces in Macedonia, Medical Research Council, Special Report Series, no. 4, London, His Majesty's Stationery Office, 1918.

7. Teague, O., and Clurman, A. W.: A Method of Preserving Typhoid Stools for Delayed Examination, J. Infect. Dis. **18**:653, 1916.

8. Bangxang, E., and Eliot, C. P.: An Investigation of Preserving Solutions for the Recovery of Dysentery Bacilli from Fecal Specimens, Am. J. Hyg. (Sect. B) **31**:16, 1940.

4.84; 30 per cent Merck reagent glycerin showed a p_H of 4.15. The most efficient of their preservatives, 1 per cent sodium citrate and 0.5 per cent sodium desoxycholate in buffered 0.9 per cent saline solution showed an average p_H of 8.76. This is particularly interesting in view of the report of Sachs,[9] who stated that the small number of positive isolations from preserved stool specimens was due to the fact that glycerin becomes acid on standing and suggested that 30 per cent glycerin be titrated to p_H 8.0 with a saturated aqueous solution of phenolsulfonphthalein in 5 per cent sodium phosphate (NH_2HPO_4). This glycerin solution, he said, can be kept for two years in screw-capped bottles and remains alkaline. At the present time glycerin prepared in such a manner in the laboratory with which I am associated has remained alkaline at room temperature for a period of ten months, including the summer, and shows no signs of a decrease in p_H.

EXPERIMENTAL STUDIES

In order to determine the effect of alkaline glycerin in preserving for a long period stools from patients known to have bacillary dysentery, 152 specimens from 88 patients were studied. Fifty-six of the patients had clinical bacillary dysentery; 12 had diarrhea; 2 had a history of diarrhea; 2 had a history of diarrhea and also had had dysentery organisms and a dwarf tapeworm found; 1 had typhoid fever; 1 had typhoid fever and bacillary dysentery; 11 had miscellaneous conditions, and for 3 no diagnosis had been made. The specimens were divided into two groups.

Group 1.—Duplicate samples were placed in test tubes. To one sample was added an equal amount of the alkaline glycerin preservative of Sachs; the other, to which no preservative was added, was divided into two and sometimes three portions. One of the unpreserved portions accompanied the preserved sample to this laboratory (laboratory 1); the others were sent to a hospital laboratory (laboratory 2), and a single specimen from each patient (a twenty-four hour specimen) was sent to a public health laboratory (laboratory 3). The hospital laboratory received its unpreserved material the same day it was taken. The preserved and unpreserved feces sent together ranged in age from one-half to four days, during which time they had been stored in the ice box. When received in this laboratory, all the feces were cultured on desoxycholate agar, desoxycholate-citrate agar and endo agar, and approximately 1 cc. of each sample was placed in a pour plate of Wilson-Blair bismuth sulfite medium. All of the preserved samples in this series were alkaline when received in the laboratory.

Table 1 shows the results. It will be noted that in 2 instances positive isolations were made from the preserved and not from the unpreserved sample of a specimen. In 2 instances only, a Salmonella was isolated

9. Sachs, A.: Difficulties Associated with the Bacteriological Diagnosis of Bacillary Dysentery, J. Roy. Army M. Corps **73**:235, 1939.

TABLE 1.—*Comparison of Bacteriologic Findings in Different Laboratories*

No. of Cases	Laboratory 1			Laboratory 2		Laboratory 3		Diagnosis
	Preserved Sample of Specimen	Unpreserved Sample of Specimen	Age of Stools, Days	Unpreserved Sample of Specimen	Age of Stools, Days	Unpreserved Sample of Specimen	Age of Stools, Days	
5	Flexner bacillus	Flexner bacillus	½-4	Flexner bacillus	½	.....	...	Clinical bacillary dysentery
1	Flexner bacillus	Negative	1	Flexner bacillus	½	.....	...	Clinical bacillary dysentery
1	Hiss bacillus	Hiss bacillus	½	Hiss bacillus	½	.....	...	Clinical bacillary dysentery
1	Strong bacillus	Strong bacillus	2	Hiss bacillus	½	.....	...	Clinical bacillary dysentery
1	Strong bacillus	Strong bacillus	½	Flexner bacillus	½	.....	...	Clinical bacillary dysentery
1	Flexner bacillus	Flexner bacillus	½-1-4	Hiss bacillus	½	.....	...	Clinical bacillary dysentery
1	Flexner bacillus	Flexner bacillus	1	No report				
1	Strong bacillus	Strong bacillus	½	Negative	½	.....	...	Clinical bacillary dysentery
1	Flexner bacillus	Flexner bacillus	1	Negative	½	.....	...	Clinical bacillary dysentery
4	Salmonella	Salmonella	½-2	Negative	½	Negative	1	Clinical bacillary dysentery
1	Salmonella	Negative	2	Negative	½	.....	...	Clinical bacillary dysentery
1	Salmonella	Exam. not done	½	Negative	½	.....	...	Clinical bacillary dysentery
2	Exam. not done	Salmonella	1	Flexner bacillus	½	.....	...	Clinical bacillary dysentery
1	Negative	Salmonella	1	Negative	½	.....	...	Clinical bacillary dysentery
3	Negative	Negative	½-3	Negative	½	.....	...	Clinical bacillary dysentery
1	Negative	Negative	½-3	Salmonella aertrycke	½	.....	...	Clinical bacillary dysentery
1	Salmonella	Salmonella	23	Negative	½	.....	...	Diarrhea
1	Negative	Salmonella	½	Negative	½	.....	...	Diarrhea

from the unpreserved sample and not from the preserved sample. Positive isolations were made in this laboratory from 6 specimens from which laboratory 2 obtained negative results. A positive culture was obtained in laboratory 2 and a negative one in this laboratory in 2 instances. In 1 of these, laboratory 2 isolated Salmonella aertrycke; in the other instance laboratory 2 isolated the Flexner bacillus while this laboratory obtained a Salmonella from the preserved specimen only.

In several instances there was disagreement between the two laboratories as to strain. With regard to 3 specimens with negative and 7 with positive cultures, there was complete agreement between the laboratories.

The finding of large numbers of strains of Salmonella is worthy of comment, since various authors have suggested that organism as the possible etiologic agent of infant diarrhea.

From these results it would appear that the preserved specimens did not give a significantly higher percentage of positive cultures than the unpreserved specimens. However, table 1 shows the differences that may appear in the reports from reliable laboratories.

Group 2.—The second group of specimens were placed in equal quantities of alkaline preservative and maintained in the ice box for varying lengths of time, from four to fifty-six days. Frequently when it was found during this time that a specimen had become acid, more alkaline glycerin preservative was added to maintain it at an alkaline p_H.

The results shown in table 2 indicate clearly the advantages, as well as the disadvantages, of preserved specimens.

The isolation of both Flexner bacilli and strains of Salmonella from preserved specimens from patients who had had no previous significant laboratory findings shows the definite advantage of preservation. A large number of strains of Salmonella were isolated from preserved specimens from patients whose stools had heretofore not yielded this organism. From the stools of 1 of these patients Eberthella typhosa had been previously isolated, and in those of another Shigella Flexner had been found. On the other hand, several specimens failed to yield dysentery bacilli when cultured after a period of twenty-two to fifty-five days although there had been previous isolations of the organisms from the patients' stools.

A large group of specimens ranging in age from three to fifty-one days were culturally sterile; the organisms were apparently killed by the alkaline preservative. Normal stools preserved in equal portions of alkaline glycerin showed growth after two months. The cultural sterility of some of the specimens in group 2 may be accounted for by the fact that these specimens were taken from patients who had received sulfanilamide or one of its derivatives.

Cultures of stock dysentery bacilli preserved in alkaline glycerin for more than two months retained their normal growth and cultural characteristics.

TABLE 2.—*Bacteriologic Observations on Preserved Specimens*

No. of Cases	Preserved Specimens	Age of Stools, Days	Previous Observation, Laboratory 2	Previous Observation, Laboratory 3	Diagnosis
1	Flexner bacillus and Salmonella	4	Negative	Negative	Clinical bacillary dysentery
1	Flexner bacillus and Salmonella	13	Negative	Negative	Clinical bacillary dysentery
1	Flexner bacillus and Salmonella	14	Negative	.....	Clinical bacillary dysentery
1	Flexner bacillus	24	Negative	.....	Clinical bacillary dysentery
1	Flexner bacillus and Salmonella	34	Hiss bacillus	Negative	Clinical bacillary dysentery
1	Salmonella	14	Flexner bacillus	.....	Clinical bacillary dysentery
1	Salmonella	10	Negative	Negative	Clinical bacillary dysentery
1	Salmonella	5	Negative	.....	Clinical bacillary dysentery
1	Salmonella	45	Negative	.....	Clinical bacillary dysentery
1	Salmonella	7	Negative	Negative	Clinical bacillary dysentery
1	Negative	27	Flexner-Strong bacillus (low titer)	Negative	Clinical bacillary dysentery
1	Negative	34	Unidentified pathogen	.....	Clinical bacillary dysentery
1	Negative	55	No report	.....	Clinical bacillary dysentery
2	Negative	24, 34, 37	Flexner bacillus	Flexner bacillus	Clinical bacillary dysentery
1	Negative	22	Negative	Negative	Clinical bacillary dysentery
1	Negative	38	Flexner bacillus	.....	Clinical bacillary dysentery
6	No growth	19, 30, 51, 42, 33, 49	Negative	.....	Clinical bacillary dysentery
1	No growth	10	Negative	Negative	Clinical bacillary dysentery
1	No growth	5, 20	Negative	Flexner bacillus	Clinical bacillary dysentery
3	No growth	28, 38, 45	Flexner bacillus	.....	Clinical bacillary dysentery
2	No growth	23, 38	Flexner bacillus	Flexner bacillus	Clinical bacillary dysentery
1	No growth	24	Strong-Flexner bacillus	Flexner bacillus	Clinical bacillary dysentery
1	No growth	28	Strong-Flexner bacillus	Negative	Clinical bacillary dysentery
2	No growth	45, 51	Strong bacillus	.....	Clinical bacillary dysentery
1	No growth	3	Salmonella aertrycke	.....	Clinical bacillary dysentery
1	Salmonella	21	Negative	Negative	Diarrhea and polyposis
1	Salmonella	43	No report	Negative	Diarrhea
1	Salmonella	8	No report	.....	Diarrhea
1	Negative	28	Salmonella	.....	Diarrhea
4	No growth	22, 34, 42, 43	Negative	Negative	Diarrhea
1	No growth	51	Salmonella	.....	Diarrhea and infection of upper respiratory tract
1	Salmonella	38	Typhoid bacillus	.....	Typhoid
1	No growth	38	.....	Typhoid and Flexner bacilli	Typhoid and dysentery
1	Negative	48	Strong bacillus	.....	No clinical dysentery

COMMENT

These results indicate, primarily, the great divergence of results which different laboratories, using different mediums, obtain in examination of stools from the same children with clinical bacillary dysentery

or diarrhea of unknown origin. The large number of strains of Salmonella, with the usual variety of cultural and biochemical reactions (so that they were not finally identified), might suggest a possible role of these organisms in diarrhea of infants and children. Finally, it is felt that these results show the advantages to be gained from the use of specimens preserved in alkaline glycerin for the isolation of dysentery bacilli, although the obvious disadvantage of the bactericidal action of that preservative must be recognized and taken into account. It is obvious that time limits in these experiments were considerably greater than would ever be used for practical purposes. This should serve to decrease the disadvantages and increase the advantages of the use of alkaline glycerin, while cultivations of unpreserved specimens will eliminate the obvious disadvantage of the lethal action of the preservative. The large number of positive cultures obtained with the preservative makes it an important aid in laboratory diagnosis of bacillary dysentery.

1853 West Polk Street.

Case Reports

SALMONELLA CHOLERAE SUIS (WELDIN) BACTEREMIA

ERWIN NETER, M.D.
BUFFALO

Paratyphoid infections of man in general and those caused by Salmonella group C in particular have not received the attention they deserve. This is due in part to the fact that the identification of Salmonella strains is rather complicated, particularly since the genus is comprised of a large number of species of different antigenic patterns. Furthermore, infections with members of the paratyphoid group cause a variety of different clinical pictures. While it is generally recognized that typhoid-like fever and gastroenteritis may be caused by members of the genus Salmonella, it is sometimes overlooked that these organisms may cause other syndromes, such as septicemia, peritonitis, cholecystitis, appendicitis, osteomyelitis and meningitis. In the following communication I should like to report some bacteriologic and immunologic observations in a case of Salmonella cholerae suis bacteremia complicating scarlet fever.

REPORT OF A CASE

E. L.,[1] a white boy 6½ years old, with a history of measles, chickenpox, whooping cough, mumps and a carbuncle on the neck, was admitted to this hospital on February 6. He was apparently well until February 4, when he began to complain of sore throat and pain in the head and back. On February 6 a rash was noted. On admission to the hospital the patient was well developed and well nourished. The pharynx was noticeably injected, and the tongue was heavily coated. Many hard, tender cervical nodes were noted at the neck. A soft systolic murmur over the apex of the heart was present. The entire body, except the face, was covered by a papular rash. The temperature was 101.5 F. (see accompanying chart). The results of the laboratory examination of blood and urine are summarized in table 1. Tuberculin and Kahn tests gave negative results. Culture of material from the throat revealed beta hemolytic streptococci in predominance. A diagnosis of follicular tonsillitis and scarlet fever was made. The patient was given sulfanilamide (5 grains every six hours). This treatment was discontinued on February 7. On February 8, sulfanilamide therapy (10 grains every four hours) was resumed, and in addition antistreptococcus serum was given. A blood culture made on February 8 revealed the presence of more than

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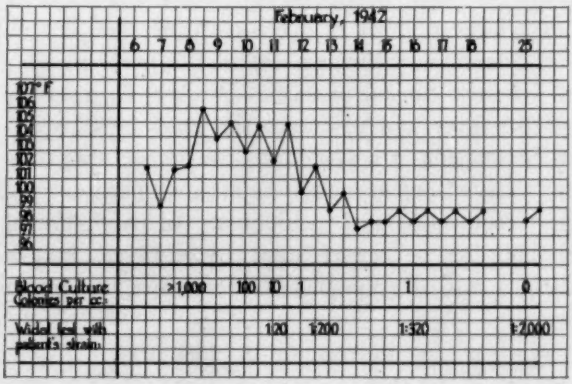
1. From the service of Dr. William J. Orr.

1,000 colonies of S. cholerae suis (Weldin) per cubic centimeter. The results of blood cultures and Widal tests are presented in detail later in this article and briefly summarized in the accompanying chart. On February 10 sulfadiazine was substituted for sulfanilamide; it was given until February 13. On February 11 another intravenous injection of the antistreptococcus serum was administered. The patient's temperature returned to normal on February 13, and he made an uneventful recovery.

The blood culture made on February 8 revealed more than 1,000 colonies of a gram-negative bacillus per cubic centimeter of blood. The organism was motile. It grew well on ordinary culture mediums, including Endo agar. The organism failed to produce indole. Following initial acidification it caused an alkaline reaction in litmus milk; litmus was not reduced. It produced acid and gas in broth containing dextrose, maltose, mannitol, xylose, rhamnose and dulcitol and failed to attack lactose and sucrose. The organism was agglutinated by Bacillus



Results of blood cultures and Widal tests in a case of S. cholerae suis bacteremia.

paratyphosus B and Bacillus aertrycke antiserums up to dilutions of 1 : 1,000, whereas Bacillus paratyphosus A and Bacillus enteritidis antiserums even in dilution of 1 : 10 failed to agglutinate this strain. The diagnostic serums were obtained from Sharp and Dohme. Through the courtesy of Dr. E. Seligmann and Dr. S. Bornstein this strain was further identified as S. cholerae suis (Weldin).

It is interesting to note that the bacteremia continued for nine days. Four consecutive blood cultures revealed the presence of the same organism. As shown in the accompanying chart, the number of colonies per cubic centimeter of blood decreased steadily during this period from more than 1,000 to less than 1. Finally, on February 25, the blood culture became negative. It may be added that para-aminobenzoic acid had been added to the blood in order to counteract any bacteriostatic effects of the sulfanilamide and sulfadiazine.

Stool cultures examined on several occasions failed to reveal the presence of Salmonella organisms.

A study of the antibody response of this patient gave the following results: On February 11 the serum of the patient in a dilution of 1:40 failed to agglutinate the patient's own strain; a weak agglutination was obtained with the serum in a dilution of 1:20. The titer of antibodies to S. cholerae suis rose to 1:200 on February 13; to 1:320 on February 16, and finally to 1:2,000 on February 25. The child was seen in the outpatient department on March 13. The titer of agglutinins at that time was 1:400. Thus it could be shown that specific antibodies in high titer developed during the course of the disease. It is interesting to note that the specimen of serum obtained on February 25 failed to agglutinate (even in a titer of 1:10) suspensions of typhoid H, typhoid O, paratyphoid A and paratyphoid B organisms and Brucella.

TABLE 1.—*Results of Examinations of Blood and Urine*

	Blood									Urine				
Date	Hemoglobin, Gm.	Red Blood Cells, per Cu. Mm.	White Blood Cells, per Cu. Mm.	Polymorphonuclears, per Cent	Juvenile Forms, per Cent	Eosinophils, per Cent	Basophils, per Cent	Lymphocytes, per Cent	Mononuclears, per Cent	Reaction	Specific Gravity	Albumin	Sugar	Microscopic Observations
2/ 7/42	16	5,400,000	5,550	36	12	4	2	44	2	Acid	1.020	0	0	Scattered white blood cells
2/ 8/42	..	.....	15,500	60	8	..	..	32	..					
2/ 9/42	..	.....	.....	..	..	..	..	..	..	Alk.	1.010	0	0	Negative
2/10/42	15	.....	14,300	40	24	..	..	32	4	Alk.	1.010	0	0	Negative
2/11/42	..	.....	.....	..	..	..	..	..	..	Acid	1.020	0	0	Scattered white blood cells
2/12/42	..	.....	...,..	..	..	..	..	..	..	Acid	.....	0	0	Few white blood cells
2/13/42	12	.....	9,700	8	20	..	..	68	4					

COMMENT

In human beings the members of the genus Salmonella cause a variety of different clinical syndromes, such as typhoid-like fever and gastroenteritis (food poisoning). In addition, they are sometimes encountered as causative agents of septicemia, endocarditis, uncomplicated bacteremia, abscesses, osteomyelitis, pleuritis, meningitis, arthritis, jaundice, cystitis and other conditions.

There can be no doubt that Salmonella infections of human beings are by no means rare. Bornstein, Saphra and Strauss [1a] identified 280 strains covering 261 from human infections in North America. More recently Bornstein [2] reported on 500 strains of Salmonella of human

1a. Bornstein, S.; Saphra, I., and Strauss, L.: Frequency of Occurrence of Salmonella Species, J. Infect. Dis. **69**:59-64 (July-Aug.) 1941.

2. Bornstein, S.: Infections with Organisms of the Salmonella Group, New York State J. Med. **42**:163-166 (Jan. 15) 1942.

origin. In Uruguay, Hormaeche and Peluffo [3] recovered Salmonella strains from 266 of 2,141 children. This represents an incidence of 12.14 per cent.

The identification of strains belonging to the genus Salmonella presents difficulties, because this genus is comprised of more than thirty-seven species with different antigenic patterns. Unfortunately, various designations are being used in medical and bacteriologic literature for a single species. It was thought desirable, therefore, to present

TABLE 2.—*The More Important Species of the Genus Salmonella*

Group	Preferred Scientific Name	Synonyms
A	S. paratyphi	B. paratyphosus A
	S. sp. (Senftenberg type)	
B	S. schottmuelleri	B. paratyphosus B
	S. typhi murium	B. aertrycke, B. pestis caviae, B. enteritidis Breslau
	S. abortivoequina	B. abortus equi
	S. abortus ovis	
	S. sp. (Chester type)	
	S. sp. (Derby type)	
C	S. cholerae suis	B. suipestifer (American type)
	S. cholerae suis (var. Kunzendorf)	B. suipestifer (European type)
	S. typhi suis	B. typhi suis Glaesser
	S. sp. (Newport type)	
	S. sp. (Oranienburg type)	
	S. sp. (Thompson type)	
	S. sp. (München type)	
	S. hirschfeldii	B. paratyphosus C
	S. sp. (Montevideo type)	
	S. sp. (Bareilly type)	
D	S. enteritidis	B. enteritidis Gaertner
	S. pullorum	
	S. gallinarum	
	S. sp. (Panama type)	
E	S. sp. (London type)	
	S. anatis	
F	S. sp. (Aberdeen type)	
G	S. sp. (Poona type)	
I	S. sp. (Hvittingfoss type)	

the more important members of the genus Salmonella in tabular form (table 2). It is important to note that the vast majority of these species may be encountered in man. Kauffmann deserves credit for a very thorough investigation of this genus. In this country Bornstein [2] found thirty-two different types among Salmonella strains of human origin. In order to determine with accuracy the incidence of the various species of the genus in different parts of the world and to establish their pathogenic significance, it seems desirable to identify as many Salmonella

3. Hormaeche, E., and Peluffo, C. A.: Salmonelliasis in Infancy and Its Diagnosis, Puerto Rico J. Pub. Health & Trop. Med. **17**:99-123 (Dec.) 1941.

strains as possible. Since many laboratories are not equipped to do this, subcultures should be sent to laboratories which specialize in the identification of Salmonella organisms.

Of the species of group C of the genus Salmonella, S. cholerae suis is probably most important. Of 77 strains belonging to this group, Bornstein and his co-workers [1a] encountered 21 strains of S. cholerae suis. This micro-organism has been responsible for many outbreaks of food poisoning.[4] The number of sporadic cases, however, seems to be relatively small according to available reports. In 1937 Harvey [4] reviewed the literature on infections of human beings caused by S. cholerae suis. He collected 50 cases proved to be such. Since then additional cases have been reported by Ravitch and Washington [5]; Kuttner and Zepp [6]; Sohier, Parnet, and Henry [7]; Herring and Nicholson [8]; Read [9]; Hardison and Shipley [10]; Bornstein, Saphra, and Strauss [1a]; Hormaeche and Peluffo [3]; Bornstein,[2] and Goulder, Kingsland, and Janeway.[10a]

The case of S. cholerae suis bacteremia reported presents several interesting features. In the first place, it should be noted that the patient was suffering from scarlet fever and that the diagnosis of a complicating Salmonella infection was made only by means of a blood culture. It is likely that the beta hemolytic streptococcic infection contributed largely to the invasion of the blood stream by the Salmonella organism. Several cases have been reported in the past in which Salmonella infections developed on the basis of other lesions. Ravitch

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4. Harvey, A. M.: Salmonella Suipestifer Infection in Human Beings: Review of the Literature and Report of Twenty-One Cases, Arch. Int. Med. **59**:118-135 (Jan.) 1937.

5. Ravitch, M. M., and Washington, J. A.: Suipestifer Septicemia and Meningitis Complicating Meningococcic Septicemia and Meningococcic Meningitis, J. A. M. A. **109**:1122-1123 (Oct. 2) 1937.

6. Kuttner, A. G., and Zepp, H. D.: Paratyphoid-Like Fever in Children Due to the Salmonella Suipestifer Group, Bull. Johns Hopkins Hosp. **51**:373-387 (Dec.) 1932.

7. Sohier, R.; Parnet, J., and Henry, R.: Ictère bénin et infection à bacille paratyphique C type Kunzendorf, Bull. et mém. Soc. méd. d. hôp. de Paris **54**: 1635-1640 (Nov. 18) 1938.

8. Herring, R., and Nicholson, W. F.: Acute Salpingitis Due to Bacterium Cholerae-Suis, Lancet **1**:1154-1155 (May 20) 1939.

9. Read, C. T.: Endocarditis Caused by Salmonella Suipestifer, J. Infect. Dis. **65**:263-266 (Nov.-Dec.) 1939.

10. Hardison, A. E., and Shipley, A. B.: Paratyphoid Septicemia in Man Due to Salmonella Suipestifer, J. A. M. A. **116**:829-830 (March 1) 1941.

10a. Goulder, N. E.; Kingsland, M. F., and Janeway, C. A.: Salmonella Suipestifer Infection in Boston: Report of Eleven Cases, with Autopsy Findings in Case of Bacterial Endocarditis Due to This Organism, and Study of Agglutination Reactions in This Infection, New England J. Med. **226**:127-138 (Jan. 22) 1942.

and Washington [5] observed a case of meningococcic meningitis in which secondarily an infection of the meninges by Salmonella occurred. In other instances, S. cholerae suis infection followed pneumonia, gonococcic urethritis, streptococcic pharyngitis, rheumatic heart disease or surgical procedures (Harvey [4]). It is likely, therefore, that in sporadic infections in human beings due to S. cholerae suis a lowered resistance plays a significant role. In this connection it is interesting to mention that in mice inborn resistance or inborn susceptibility are decisive for the outcome of experimental infections with Salmonella enteritidis (Webster and Hodes [11]). On the other hand, the virulence of the particular organism is important. Pike and MacKenzie [12] made the interesting observation that strains of Salmonella typhi murium may vary significantly in their virulence, although they may possess similar degrees of invasiveness. These investigators found that an invasive strain which produces a fatal infection in mice is able to multiply in the host, whereas an equally invasive strain which does not produce a fatal infection fails to do so. It seems likely that in the case of S. cholerae suis bacteremia reported here the causative organism was an invasive strain of relatively low virulence. The fact that the bacteremia persisted for many days does not invalidate this assumption. Experimentally, it was shown that certain Salmonella strains of low virulence may survive in organs for relatively long periods (Pike and MacKenzie [12]).

The case of S. cholerae suis bacteremia reported is interesting also because of the large number of organisms in the circulating blood. More than 1,000 bacteria per cubic centimeter of blood were present at the beginning of the illness. In his review of the literature Harvey [4] found that the largest number of organisms per cubic centimeter of blood in any culture then recorded was 255. In this instance the patient died.

The question as to whether or not chemotherapy with sulfanilamide and sulfadiazine contributed to the recovery of the patient reported on here cannot be answered with certainty. It is interesting to note that both in vitro and in vivo sulfaguanidine is effective against S. cholerae suis and Salmonella paratyphi A; in contrast, this drug is ineffective against other species of this genus (Bornstein and Strauss [13]). It is evident that sulfaguanidine should not be used in the treatment of

11. Webster, L. T., and Hodes, H. L.: Role of Inborn Resistance Factors in Mouse Populations Infected with Bacillus Enteritidis, J. Exper. Med. **70**:193-208 (Aug.) 1939.

12. Pike, R. M., and MacKenzie, G. M.: Virulence of Salmonella Typhimurium, J. Bact. **40**:171-195 (Aug.) 1940.

13. Bornstein, S., and Strauss, L.: Selective Action of Sulfanilyl-Guanidine on Different Salmonella Types and Its Practical Importance, Proc. Soc. Exper. Biol. & Med. **47**:112-115 (May) 1941.

an infection of the blood stream. Libby [14] showed that in vitro sulfathiazole and sulfapyridine exert bacteriostatic activity against B. paratyphosus A, and Weil and Gall [15] reported that sodium sulfathiazole is effective against Salmonella pullorum infection of chick embryos. Trevett, Nelson and Long [16] observed 1 case of Salmonella aertrycke bacteremia; on treatment with sulfadiazine the patient improved.

The study of the antibody response to the infection with S. cholerae suis revealed several interesting facts. In the first place, it was shown that at the onset of the disease the titer of agglutinins was low (1:20). During the course of the illness the agglutinin titer gradually increased, and it finally reached 1:2,000 approximately two and a half weeks after the onset of the illness (see chart). Two examinations, forty-eight hours apart, revealed an increase from 1:20 to 1:200. This occurred approximately one week after the onset of the illness. It is of practical importance to mention that the patient's serum failed to agglutinate B. paratyphosus A and B. paratyphosus B suspensions. It is evident, therefore, that without the inclusion of the B. paratyphosus C suspension the Widal test would have yielded negative results. It seems advisable to include B. paratyphosus C suspensions as antigens routinely in the Widal test for the diagnosis of Salmonella infections.

SUMMARY

A case of S. cholerae suis bacteremia complicating scarlet fever is presented. The number of bacteria present in the blood was unusually large. The patient recovered completely after treatment with sulfanilamide and sulfadiazine. Specific agglutinins in high titer developed during the course of the illness.

Drs. S. Bornstein, J. Saphra and E. Seligmann, of Beth Israel Hospital, New York, identified the Salmonella strains recovered from patients at this hospital in the past.

219 Bryant Street.

14. Libby, R. L.: The Activity of Chemotherapeutic Agents, J. Bact. **40**: 733-745 (Nov.) 1940.

15. Weil, A. J., and Gall, L. S.: Chemotherapeutic Testing with Sodium Sulfathiazole in the Developing Chick Embryo, J. Infect. Dis. **69**:97-101 (Sept.-Oct.) 1941.

16. Trevett, G. I.; Nelson, R. A., and Long, P. H.: Studies on Sulfadiazine: II. The Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections, Other than Pneumonia, Bull. Johns Hopkins Hosp. **69**:303-313 (Oct.) 1941.

BOECK'S SARCOID WITH NODULAR IRITIS IN A CHILD

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Boeck's sarcoid is a chronic relatively benign disorder of unknown cause with particular predilection for the lymph nodes, lungs, skin and bones; less frequently, there is involvement of the liver, spleen, kidneys, eyes, brain or meninges. It was first described by Boeck [1] in 1899 as an entity in which the cutaneous lesions simulated sarcomas and leukemic conditions of the skin. In 1914 Shaumann [2] reported that the condition might involve any organ of the body, with or without cutaneous lesions.

The disease affects young adults of either sex. Most of the patients reported on have been of the white race, except for the series reported by Longcope and Pierson [3] and Harrell,[4] in which Negroes predominated. It is rare in children and in them has involved primarily the skin, lymph nodes, lungs and bones. Roos [5] described a case of Boeck's sarcoid in a girl, 4 years of age who had lesions in the skin, liver, spleen, kidneys, lymph nodes and brain. He cited from the literature 9 other undoubted cases in which the disease occurred in children. All but 2 of the children were over 6 years of age and had cutaneous lesions; 5 had cystic changes in the bones; 2 had enlargement of the lymph nodes, and in 2

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Dr. George Margolis prepared the pathologic sections, Dr. George J. Baylin the roentgenograms and Mr. Elon H. Clark the drawings of the eye.

1. Boeck, C.: Multiple Benign Sarcoid of Skin, J. Cutan. & Genito.-Urin. Dis. **17**:543, 1899.

2. Shaumann, J.: Lupus Pernio: Study on Lupus Pernio and Its Relationship to Sarcoids and Tuberculosis, Ann. de dermat. et syph. **6**:357, 1916.

3. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223, 1937.

4. Harrell, G. T.: Generalized Sarcoidosis of Boeck: A Clinical Review of Eleven Cases with Studies of the Blood and the Etiologic Factors, Arch. Int. Med. **65**:1003 (May) 1940.

5. Roos, B.: Occurrence of Schaumann's Benign Lymphogranulomatosis (Boeck's Benign Sarcoid) in Children, Ztschr. f. Kinderh. **59**:280, 1937.

others there was enlargement of the mediastinal lymph nodes. Muller [6] reported the case of a 12 year old girl with involvement of the lymph nodes, lungs and phalanges. Naumann [7] described 2 cases, one with sarcoid formations in the falx and tentorium cerebelli and the other with pulmonary involvement. Newns and Hardwick [8] reported on a 2 year old boy with spindle-shaped swellings of the fingers and cystic changes in the phalanges.

Snapper and Pompen [9] stated that the eye is one of the favorite sites of the disease. In a survey of the literature this has not been found true in children. Because of the rarity of ocular lesions in children this case is presented.

REPORT OF A CASE

History.—J. R., a 9 year old Negro girl, was admitted to Duke Hospital on Nov. 30, 1941, because of "a sore eye." The family and past histories were irrelevant. Two months before admission the child suddenly complained of "smarting and stinging" of the left eye. No foreign body was seen on examination. Within three days the inflammatory process had subsided, only to recur several times during the following month. Three weeks prior to admission the ocular symptoms reappeared; the eye became inflamed; there was increased lacrimation, and vision seemed impaired in the left eye. All the ocular symptoms persisted and gradually increased in severity until her admission to the hospital.

Physical Examination (Fig. 1).—Her temperature was 37.8 C. (100 F.), her pulse rate 108, her respiratory rate 20 and her blood pressure 120 systolic and 72 diastolic. The patient was a poorly developed and poorly nourished girl, who did not appear ill. She was mentally alert and cooperative. Her weight was 18.25 Kg. (40.1 pounds) and her height 123 cm. (49 inches). The skin was dry, warm and shiny and had no lesions. The anterior and posterior cervical, submaxillary, axillary, epitrochlear and inguinal nodes were small, nontender, discrete and rubber-like. The tonsils were moderately enlarged and hyperemic. The examination of the heart, lungs and abdomen showed nothing abnormal.

Ocular Examination.—The vision in the right eye was 20/20 and in the left eye 20/400. The lids and lashes were normal. The excursion of the globes was unrestricted and equal. No ptosis or nystagmus was present.

The Right Eye: The cornea was clear. The pupil was round and regular and reacted to light and in accommodation. It dilated well with 1 per cent

6. Muller, R. W.: Generalized Miliary Lupoid in Child, Monatschr. f. Kinderh. **72**:34, 1938.

7. Naumann, O.: Schaumann's "Benign Granulomatosis" (Besnier-Boeck-Schaumann Disease): Case in Infant, Ztschr. f. Kinderh. **60**:1, 1938.

8. Newns, G. H., and Hardwick, C.: Besnier-Boeck's Disease in an Infant, Arch. Dis. Childhood **14**:78, 1939.

9. Snapper, I., and Pompen, A. W.: Pseudo-Tuberculosis in Man: I. Besnier-Boeck's Disease, Haarlem, de Erven F. Bohn, 1938.

homatropine hydrobromide solution. The lens and vitreous were clear. The fundus was essentially normal.

The Left Eye (Fig. 2): The lower half of the cornea was diffusely hazy owing to grayish white superficial amorphous deposits or metaplasia on the cornea. At the temporal and nasal limbus was a clear area of cornea 0.5 mm. in diameter. Extending over the lateral and medial limbus were seen similar amorphous deposits in the conjunctiva. On the posterior surface of the cornea were many large mutton fat keratitic precipitates. The aqueous flare was greatly exaggerated.

Fig. 1.—General nutrition of a patient with Boeck's sarcoid.

Many cells were seen in the upper portion of the involved cornea. The pupil was irregular and eccentric owing to posterior synechias. There were many large nodules, varying from 1 to 3 mm. in diameter, located on both the pupillary and the attached border of the iris; these nodules protruded into the anterior chamber. Some of the cystic nodules were filled with clear fluid and were devoid of pigmentation. They showed evidence of vascularization. Areas of atrophy and thinning were present throughout the entire iris. The lower angle of the anterior chamber was obliterated by an amorphous deposit resembling iris pigment which

Fig. 2.—Drawing of the nodules in the iris and pigment deposits on the anterior surface of the lens as viewed with a slit lamp.

UNIV. OF MICH.

had become organized and then vascularized. One large vessel was plainly seen on the surface of the deposit. There were many scattered pigmented deposits on the anterior surface of the lens. The posterior segment could not be visualized.

Laboratory Examination.—On the patient's admission to the hospital, the hemoglobin content was 12.4 Gm. per hundred cubic centimeters (80 per cent). The red blood cell count was 5,200,000, and the white blood cell count, 8,840, with 76 per cent polymorphonuclear leukocytes (of which 59 per cent were segmented forms, 13 per cent nonsegmented and 4 per cent eosinophils), 7 per cent large lymphocytes, 15 per cent small lymphocytes and 2 per cent monocytes. The corrected erythrocyte sedimentation rate ranged from 4 to 10 mm. in the first hour. The Weltmann reaction revealed a coagulation band of six. The "formol-gel" test showed barely perceptible coagulation; the control was negative. The response to repeated Wassermann tests was negative. The serum calcium was 10.4 mg. per hundred cubic centimeters, the total plasma protein 6.5 Gm., the albumin 3.3 Gm. and the globulin 3.2 Gm. (albumin-globulin ratio, 1.0). Examinations of the urine and stools showed them to be normal. Intradermal tuberculin tests with dilutions of 1:1,000,000 to 1:100 gave negative results.

Repeated examinations of the sputum and of gastric washings gave negative results for acid-fast bacilli and fungi. Two guinea pigs were inoculated with extracts of an excised lymph node and 2 were inoculated with sputum. No gross lesions of tuberculosis were observed in any of these animals at postmortem examination, and the reactions to tuberculin tests were negative.

Roentgenograms (Figs. 3 and 4).—Chest: The pulmonary fields were studded with a rather indefinite mottling which appeared to be interstitial. There was a striking enlargement of the superior mediastinum, with bilateral, symmetric enlargement of the hilar lymph nodes. The right interlobar fissure was thickened. The diaphragms were normal.

Feet and Hands: No definite cystic changes could be seen.

Long Bones and Skull: These were normal.

Microscopic Examination of an Axillary Lymph Node (Figs. 5 and 6).—The normal structure was replaced entirely by discrete tubercles consisting of epithelioid cells, some of which showed some hyalinization. In the center of some of these tubercles were giant cells containing as many as twenty nuclei. However, no caseation was seen in any of the tubercles. No tubercle bacilli could be found in preparations treated with the Ziehl-Neelsen stain. The pathologic report was Boeck's sarcoid.

Clinical Course.—The patient was given a high calory, high vitamin diet containing cod liver oil, ascorbic acid, thiamine hydrochloride and brewers' yeast. One drop of 0.5 per cent atropine sulfate solution was used in the left eye three times daily. During the hospital stay of four weeks the child had a low grade elevation of temperature to 37 to 38.1 C. (98.5 to 100.4 F.) but seemed to feel fine, ate well and gained 750 Gm. (1½ pounds) in weight. The condition of the left eye remained essentially the same throughout the hospitalization; no improvement was noted at discharge.

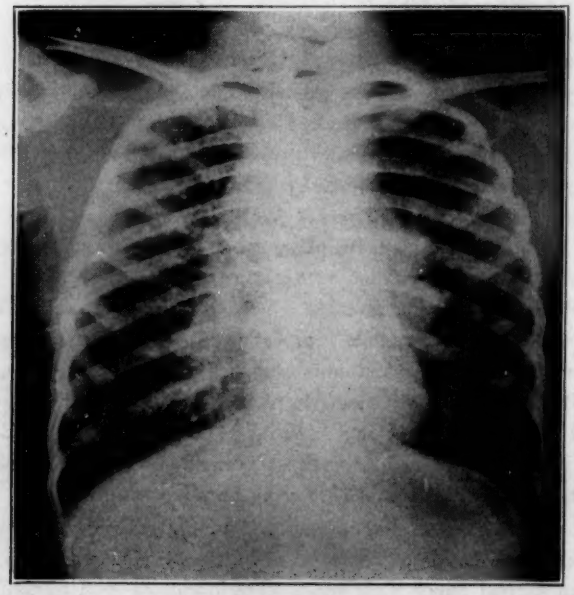

Fig. 3.—Bilateral symmetric enlargement of the hilar lymph nodes and a diffuse infiltration of the lungs.

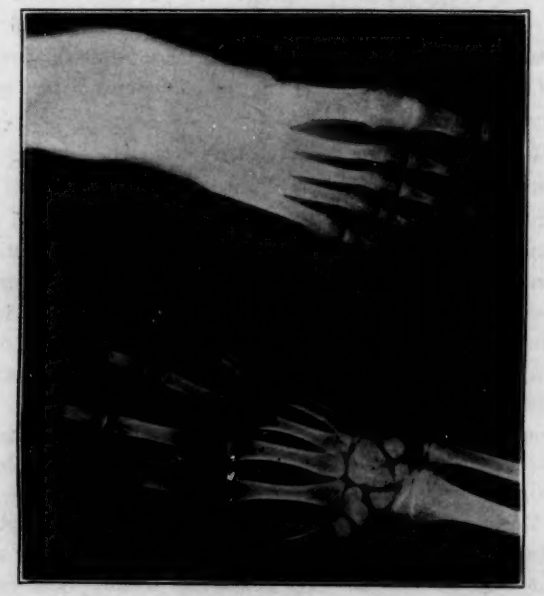

Fig. 4.—Roentgenograms of the hand and foot showing no cystic areas of rarefaction.

Follow-Up.—One month after discharge the patient had gained 300 Gm. (10 ounces) on a very inadequate diet. She had been feeling well and attending school. The general physical examination gave the same results as on her admission to the hospital. The vision in the left eye was unimproved. The corneal haze and descemetitis had cleared somewhat. There was evidence of vascular-

Fig. 5.—Photomicrograph (low power) of a section of an axillary lymph node showing many tubercles without caseation.

ization on the posterior surface of the cornea. The pupil was poorly dilated owing to posterior synechias. The large cystic nodules on the iris had completely cleared. In the iris on the nasal side were four pinhead-sized yellow granules clustered together. Pigmented deposits were still present on the anterior surface of the lens. The posterior segment could not be visualized. Reexamination

of the chest showed considerable regression of the enlargement of the lymph nodes, but the peripheral lung fields showed as much, or possibly slightly more, mottling than on previous examinations. Roentgenograms of the hands, feet and long bones still revealed no cystic changes.

Fig. 6.—Photomicrograph (high power) of the section in figure 5, showing discrete tubercles consisting of epithelioid and giant cells with hyalinization of the connective tissue.

SUMMARY

A case of ocular involvement in a Negro girl of 9 years is reported. The differential diagnosis was: (1) tuberculous iritis, (2) syphilitic iritis and (3) Boeck's sarcoid. By means of physical examination, roentgenograms, intradermal tuberculin and Wassermann tests, repeated

examinations of the sputum, inoculations of guinea pigs and histologic studies of a lymph node, the diagnosis of Boeck's sarcoid was established. The course of Boeck's sarcoid is protracted and characterized by a remarkable tendency toward healing. It rarely is fatal.[10]

Duke Hospital.

10. Levitt, J. M.: Boeck's Sarcoid with Ocular Localization, Arch. Ophth. **26**:358 (Sept.) 1941.

NUTRITIONAL ANEMIA IN AN INFANT RESPONDING TO PURIFIED LIVER EXTRACT

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Macrocytic hyperchromic anemia in infancy is infrequently observed. Faber [1] and Bachman [2] have reviewed 19 previously reported cases. Langmead and Doniach [3] recorded an additional case. Macrocytic hyperchromic anemia in infancy usually is observed in previously healthy infants after an infection of the upper respiratory tract followed by a period of vomiting or diarrhea or both. The patients are noticeably malnourished and fail to gain weight in spite of changes in formulas and addition of various vitamins to the diet. Free hydrochloric acid is nearly always present in the gastric contents, although frequently decreased in amount. Administration of crude liver extract by mouth or injection has frequently been followed by reticulocytosis, rapid rise in the number of red blood cells and gain in weight. Anemia does not recur after it has once been relieved.

Because of the comparative rarity of this type of anemia, the case of a child of 4 months in whom it was observed is here presented:

REPORT OF A CASE

A white girl aged 4 months entered the hospital on Feb. 13, 1941 because of refusal to take her food and because of loss of weight. She had been a full term baby, normally delivered, weighing 6¾ pounds (3,062 Gm.). Because of previous toxemia the mother had mistakenly eaten no meat during the period of gestation. At 2 months the baby had weighed 8½ pounds (3,856 Gm.) and appeared normal. Vomiting of increasing frequency began shortly after onset of the infection of the upper respiratory tract. During the week preceding her entry to the hospital

From the Lilly Laboratory for Clinical Research and the Indianapolis City Hospital.

1. Faber, H. K.: Value of Liver Extract (343) in Identifying and in Treating Certain Anemias of Infancy and Childhood: Report of Case of Probable Primary Anemia in Infant Nine and One-Half Months Old, Am. J. Dis. Child. **36**:1121 (Dec.) 1928.

2. Bachman, A. L.: Macrocytic Hyperchromic Anemia in Early Infancy: Report of Case and Review of Literature, Am. J. Dis. Child. **52**:633 (Sept.) 1936.

3. Langmead, F. S., and Doniach, I.: Pernicious Anemia in Infant, Lancet **1**: 1048 (May 1) 1937.

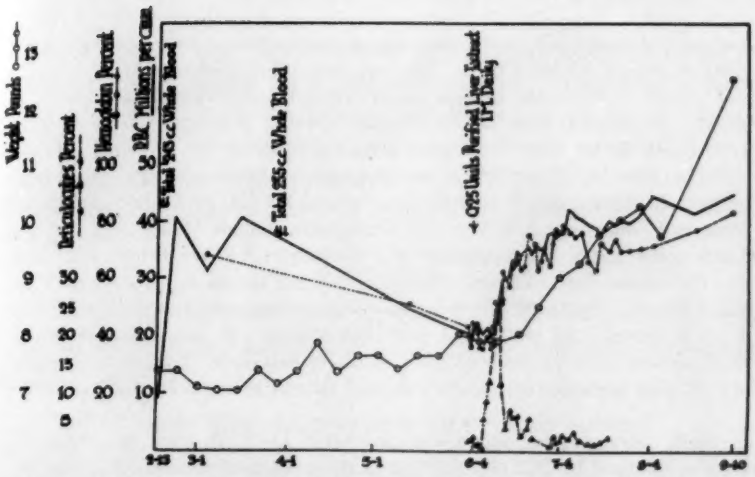

Fig. 1.—Response of red blood cells, hemoglobin, reticulocytes and weight to daily administration of purified liver extract.

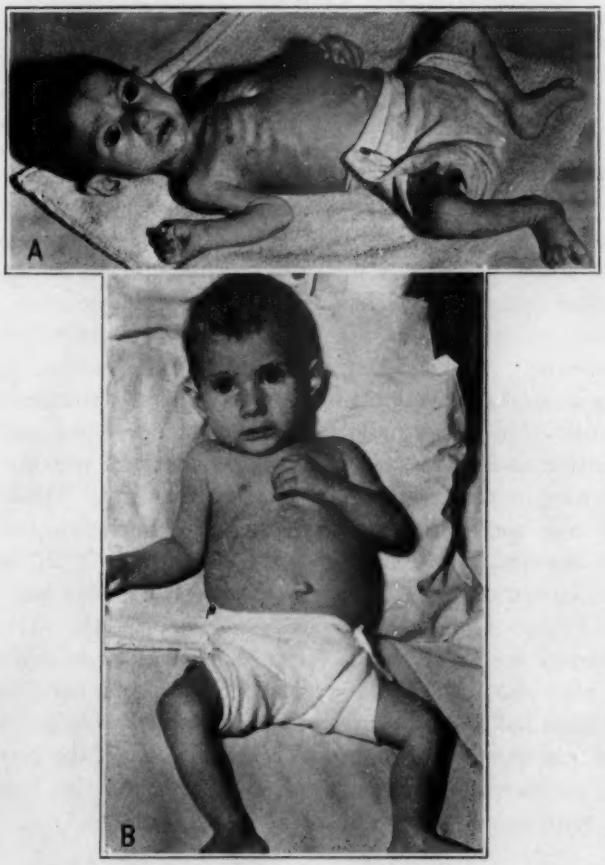

Fig. 2.—(*A*) The patient on June 10, 1941, six days after start of liver therapy. (*B*) The patient on August 6, two months after institution of liver therapy.

she had refused nearly all food. She was distinctly malnourished, weighing only 7 pounds 6 ounces (3,348 Gm.). The red blood cell count was 910,000. She received a total of 478 cubic centimeters of whole blood between February 14 and March 13. In addition, iron and ammonium citrates, brewers' yeast and various preparations of the vitamin B complex were administered, all of which were discontinued by May 14. The formula was changed frequently, but she failed to gain and by June 3 weighed only 7 pounds 13 ounces (3,374 Gm.) (fig. 1). By then the red blood cell count was 1,790,000, the hemoglobin content 36 per cent, the white blood cell count 5,700, the percentage of reticulocytes 1.8, the hematocrit reading 16.5 cc., the volume index 1.0, the color index 1.0 and the mean corpuscular volume 92 cubic microns. On smear the red blood cells varied greatly in size, many being larger than normal and well filled with hemoglobin. It was assumed that the macrocytosis was more pronounced prior to the transfusions. Gastric analysis done on June 27 after histamine stimulation showed normal amounts of free hydrochloric acid.

The daily intramuscular administration of 0.25 U. S. P. units of purified liver extract was followed by 26.8 per cent rise in the number of reticulocytes (fig. 2*A*). This reticulocytosis was followed by a pronounced clinical improvement, rise in red blood cells and gain in weight (fig. 2*B*). After three months of administration of liver extract the weight of the child was 12 pounds 8 ounces (5,670 Gm.), the red blood cell count 4,480,000 and the hemoglobin content 83 per cent. Improvement continued, and after nine months of therapy the weight was 22 pounds (9,979 Gm.), the red blood cell count 4,500,000 and the hemoglobin content 85 per cent.

COMMENT

A macrocytic hyperchromic anemia, other than pernicious anemia, can develop when the extrinsic factor of Castle is absent from the diet or the antianemic material is not absorbed from the gastrointestinal tract, as in sprue, pellagra (some cases), celiac disease, tropical anemia and intestinal anastomosis. Failure of storage of the active principle in the liver, as in cirrhosis, likewise can produce macrocytic hyperchromic anemia. The deficient diet taken by the mother during the period of gestation supplied only minimal amounts of antianemic material for the fetus. The anemia and loss of weight developed quickly after slight infection and decreased intake of food. There was no improvement following administration of iron and vitamins. Apparently the deficiency was specific for the hepatic anti-pernicious-anemia factor. The small amounts of the highly purified liver extract did not supply any of the known components of the vitamin B complex but contained 0.25 U. S. P. unit of liver anti-pernicious-anemia principle. The response to this therapy was very satisfactory. The reticulocyte count of 26.8 per cent was maximal, and the gain in red blood cells was rapid. Whereas there had been an increase in weight of 7 ounces (198 Gm.) during the four months in the hospital before starting of the liver therapy, there was an increase of 7 pounds 7 ounces (3,364 Gm.) during the following four months.

Previous investigators have usually employed powdered liver extract administered orally in the treatment of macrocytic hyperchromic anemia of infancy. Since such an extract contains many of the vitamins, it has been impossible to determine whether the therapeutic effect is due to the anti-pernicious-anemia principle or to the vitamins. Our observations indicate that the response is to the antianemic principle.

SUMMARY

An infant having nutritional anemia responded to daily injections of purified liver extract containing 0.25 U. S. P. unit of anti-pernicious-anemia principle.

Dr. James C. Carter gave us permission to report on this patient.

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Progress in Pediatrics

PHYSIOLOGIC HANDICAPS OF THE PREMATURE INFANT

I. THEIR PATHOGENESIS

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The newly born infant must make a number of physiologic adjustments in transit from a parasitic intrauterine to an independent extrauterine existence. The infant who is born at term is usually able to make these adjustments successfully, and in consequence his chances of survival are good. On the other hand, the physiologic immaturity of the prematurely born infant renders his organism less well equipped to cope with the external hazards encountered at birth, with the result that his capacity for satisfactory adaptation is low and his neonatal mortality correspondingly high. It is estimated that of the 2,000,000 full term babies born each year in the United States 95 or 96 of every 100 reach their first birthday, whereas not more than 65 or 70 of every 100 of the 100,000 premature babies born annually survive their first year. The importance of prematurity as a cause of death in the newborn period is graphically illustrated in figure 1, prepared by the Children's Bureau.

In 1937, practically one half of all neonatal deaths (47 per cent) were attributable to prematurity; 35 per cent were due to birth injuries, congenital malformations and other prenatal and natal conditions, such as maternal narcosis, premature placental separation, malposition of the fetus in utero and prolapsed cord, and a smaller proportion (18 per cent) to a miscellaneous group of postnatal conditions.

For purposes of reference a number of the outstanding handicaps exhibited by premature infants are listed in table 1.

The table is arranged to show the common handicaps with the usual symptoms resulting from their pathologic exaggeration. Premature infants exhibit difficulties of respiration which predispose them to

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Benjamin Knox Rachford Lecture, delivered by S. Z. Levine at Cincinnati, Oct. 23, 1941.

From the Department of Pediatrics, Cornell University Medical College, and the New York Hospital.

asphyxial attacks and aspiration pneumonia. Circulatory difficulties are manifested by cyanosis of the extremities and frequent edema. Faulty control of body temperature facilitates the development of hypothermia and hyperthermia. A diminished tolerance of the alimentary apparatus predisposes to gastrointestinal upsets. An increased fragility of the capillaries contributes to the high incidence of hemorrhage. Impairment of renal function leads to the frequent occurrence of dehydration and acidosis. Inadequate antenatal storage of minerals and vitamins explains the predilection of premature infants to rickets, scurvy and anemia; a similar inadequacy of placental transmission of immune

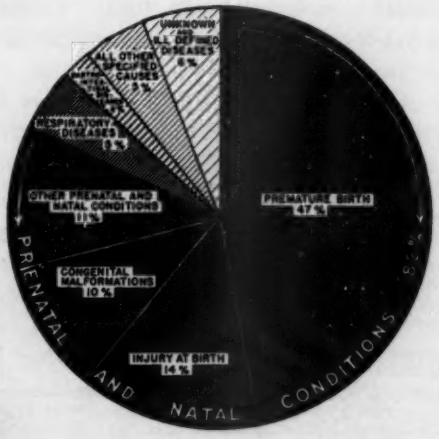
UNKNOWN AND ILL DEFINED DISEASES 6%
ALL OTHER SPECIFIED CAUSES 3%
RESPIRATORY DISEASES 8%
OTHER PRENATAL AND NATAL CONDITIONS 11%
CONGENITAL MALFORMATIONS 10%
INJURY AT BIRTH 14%
PRENATAL AND NATAL CONDITIONS 95%
PREMATURE BIRTH 47%

Fig. 1.—Causes of neonatal mortality in the United States in 1937.

TABLE 1.—*Handicaps of the Premature Infant*

Physiologic Manifestations	Pathologic Exaggerations
1. Difficulties of respiration	Asphyxial attacks, aspiration pneumonia
2. Difficulties of circulation	Cyanosis of extremities, edema
3. Faulty control of body temperature	Hypothermia and hyperthermia
4. Diminished alimentary tolerance	Gastrointestinal upsets
5. Increased capillary fragility	Hemorrhage
6. Impairment of renal function	Dehydration and acidosis
7. Inadequate antenatal storage	
Minerals and vitamins	Rickets, scurvy, anemia
Immune substances	Infections
8. Defective hemopoiesis	Anemia
9. Hepatic immaturity	
Bilirubinemia	Jaundice
Hypoglycemia	Shock
Hypoproteinemia	Edema
Hypoprothrombinemia	Hemorrhage
10. Increased content of body water	Infections, edema
11. Incomplete development of enzyme systems	Absence of creatinuria, faulty metabolism of aromatic amino acids, impaired formation of hemoglobin

substances, their heightened susceptibility to infections. A defective hemopoietic function also contributes to anemia. Hepatic immaturity superimposed on an increased destruction of blood is manifested by a high level of bilirubinemia and frequent visible jaundice, by hypoglycemia which predisposes to shocklike symptoms, by hypoproteinemia predisposing to edema and by hypoprothrombinemia and frequent hemorrhage. The hydrolability of such infants probably plays a contributory role in the high incidence of edema and infections. Finally, an incomplete development of enzyme systems may explain the low output of creatine in the urine, the faulty metabolism of aromatic amino acids, the impaired synthesis of hemoglobin and other metabolic aberrations.

The multiplicity of these handicaps, not all of which are listed, precludes their detailed consideration in toto. In this paper I shall enumerate the physiologic factors underlying these handicaps and limit

TABLE 2.—*Immaturity of the Systems Involved in Respiration*

System	Evidence of Immaturity	
1. Nervous	A high threshold of the respiratory center requires stronger afferent stimuli for response; in addition, weak gag and cough reflexes facilitate aspiration of foreign material into the respiratory passages	
2. Vascular	Reduced vascularity of the pulmonary capillaries impedes gaseous exchanges	
3. Pulmonary	A sparsity of elastic tissue prolongs physiologic atelectasis and causes a delayed expansion of the pulmonary alveoli	
4. Muscular	Feeble tonus and weak movements of the intercostal muscles and diaphragm	Lead to a reduced negative intrathoracic pressure
and		
5. Skeletal	Softness and pliability of the bones of the thoracic cage	
6. Hematologic	Possibly a persistence of the fetal type of hemoglobin may lower the uptake of oxygen at the high oxygen tensions present in the lungs at birth	

the discussion in the main to those physiologic peculiarities which have been subjects of special study in the pediatric clinic and laboratories of the Cornell Medical College and the New York Hospital. This work represents a joint undertaking of the members of the pediatric staff of these institutions with assistance from the Children's Bureau.

A prominent example of the general immaturity of the premature infant is the incomplete development of his respiratory apparatus at birth. His respirations are rapid, shallow and frequently irregular, often with prolonged periods of apnea. Attacks of cyanosis may be induced in him by causes so trivial as to be without consequence in infants born at term. The physiologic basis for his respiratory difficulties is the underdevelopment of at least five, and possibly more, of his bodily systems.

Evidence of the low reactivity of the respiratory center of premature infants was obtained by Dr. Louis Weymuller and myself by attaching a pneumograph around the chests of premature and full term infants, exposing them to varying concentrations of carbon dioxide in a respi-

ration chamber and recording the respiratory movements on a smoked drum (unpublished data).

The breathing of a full term infant of 7 pounds (3,175 Gm.) in room air containing about 0.04 volumes per cent of carbon dioxide was regular. Exposure to an increased concentration of as little as 0.7 per cent produced a slight but definite increase in the amplitude of respirations, and a further augmentation to 1.5 per cent resulted in pronounced stimulation of both the rate and the depth of breathing. In contrast to these results showing the responsiveness of the respiratory center of the full term infant to relatively slight elevations of carbon dioxide were the results obtained with premature infants.

The breathing of a 10 day old premature infant of 4½ pounds (2,041 Gm.) in an atmosphere of 0.22 volumes per cent of carbon dioxide was rhythmic and shallow. A tenfold increase to 2.4 per cent produced a slight increase in the amplitude of respirations, but not until the concentration of carbon dioxide had been raised to the high level of 3.9 per cent did the rate and depth of respiration increase greatly. Reexposure to the initial level of atmospheric carbon dioxide was accompanied by a return to the shallow respiratory movements observed in the control period.

The breathing of 2 other premature infants in room air was of the Biot type, with frequent periods of apnea. The first of these infants, who weighed less than 2½ pounds (1,134 Gm.), continued to breathe irregularly until the carbon dioxide content of the surrounding air had been raised to 4.2 per cent, and the irregularity returned when he was reexposed to room air. The second, and larger, infant, who weighed 5 pounds (2,268 Gm.), showed an essentially similar response. The irregular breathing with periods of apnea persisted until the carbon dioxide content of the air had been raised to 3.5 and 4.3 per cent respectively, and subsequent reexposure to room air resulted in a prompt return to aperiodic breathing.

The difference in response of premature and full term infants to similar tensions of carbon dioxide probably depends on a lowered sensitivity of the respiratory center of the premature infant to chemical stimulation. Whether this difference in sensitivity is neurogenic in origin, that is, dependent on different degrees of development of the nerve cells or their enzymes, or whether it is on a vascular basis, due to an impoverished capillary supply impeding gaseous exchanges between the blood and the center, is not certain. That the latter probably plays a role is suggested by figure 2, which portrays the capillary development of the medulla oblongata in infants of different weights. This figure, which is a reproduction of photomicrographs prepared by the method of Sjöstrand, shows in a striking manner the progressive enrichment

of the vascular supply of the medulla of infants whose weights ranged from 1.0 to 2.0 Kg. and from 2.5 to 3.4 Kg.[1]

This correlation between the degree of vascularization of the capillaries and the birth weight of infants was also demonstrated by Klemola [2] in a study of the structure of the lungs. Figure 3, reproduced from his work, shows the striking differences in number and vascularity of the pulmonary capillaries of stillborn infants ranging in weight from 0.5 to 1.0 Kg. and from 2.3 to 3.4 Kg. The impoverished pulmonary vascular bed of premature infants explains in part the impediment to gaseous diffusion and the tendency to cyanosis.

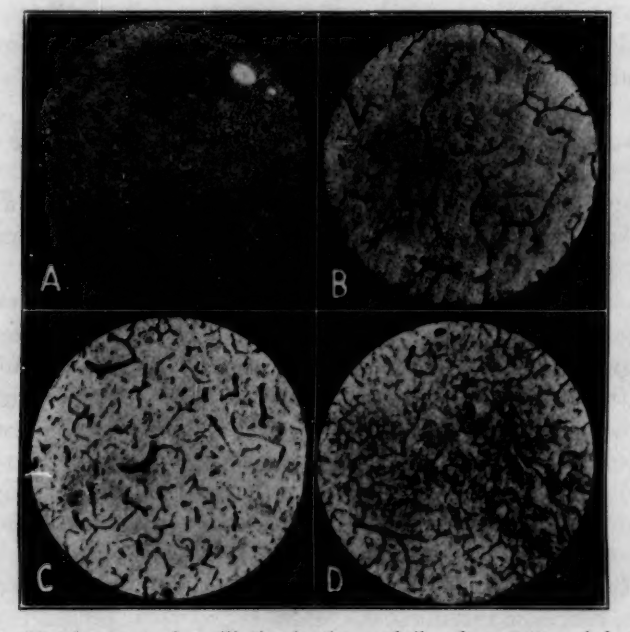

Fig. 2.—Development of capillaries in the medulla of premature infants: (*A*) of an infant weighing 1 Kg.; (*B*) of an infant weighing 2 Kg.; (*C*) of an infant weighing 2.5 Kg., and (*D*) of an infant weighing 3.4 Kg. (From Mali and Räihä.[1])

Figure 4, obtained from the same source, portrays analogous differences of development of the elastic tissue of the lungs of premature and

1. Mali, A. M., and Räihä, C.-E.: Vergleich zwischen dem Kapillarnetz des Frühgeborenen und dem des reifen Kindes und über die Bedeutung des unentwickelten Kapillarnetzes bei der Entstehung gewisser bei Frühgeburten vorkommender Eigenschaften, Acta pædiat. **18**:118, 1935.

2. Klemola, E.: Ueber den Lungenbau der Frühgeburt und des ausgetragenen Kindes, vor allem mit Rücksicht auf die Entwicklung der elastischen Fasern und der Kapillaren, Acta pædiat. **21**:236-249, 1937.

of full term infants. The premature infant, who weighed 1.6 Kg. at death, exhibited a pronounced sparsity of pulmonary elastic tissue; the full term infant, who weighed 3.4 Kg., possessed an abundance of these fibers. This paucity of pulmonary elastic tissue is undoubtedly an

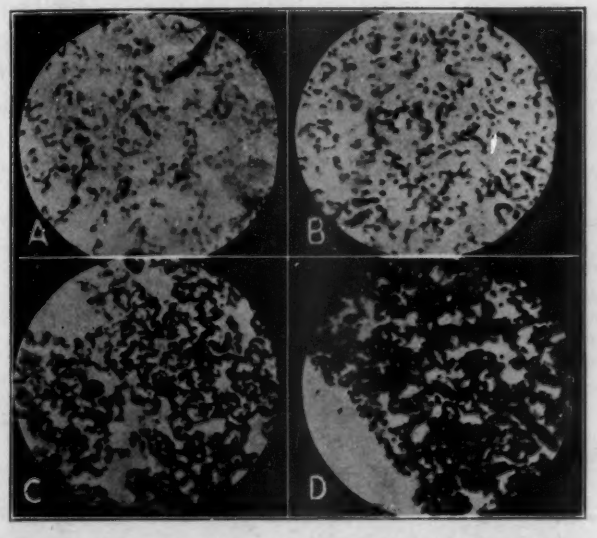

Fig. 3.—Development of capillaries in the lungs of stillborn infants: (*A*) of an infant weighing 0.5 Kg.; (*B*) of an infant weighing 1 Kg.; (*C*) of an infant weighing 2.3 Kg., and (*D*) of an infant weighing 3.4 Kg. (From Klemola.)

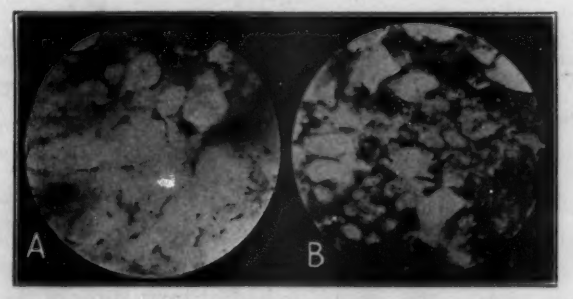

Fig. 4.—Development of elastic fibers in the lungs of (*A*) a premature infant weighing 1.6 Kg. at death, when 8 days old, and (*B*) of a full term infant weighing 3.4 Kg. at death, when 3 days old. (From Klemola.[2])

important factor contributing to the high incidence of persistent atelectasis in premature infants.

These anatomic imperfections, the high threshold of excitability of the respiratory center, the reduced negative intrathoracic pressure,

dependent on a feeble musculature and a soft bony cage, and the incomplete development of other systems, together with the high incidence of intracranial hemorrhage and aspiration of foreign material into the respiratory passages, combine to explain on morphologic and physiologic grounds the respiratory difficulties encountered by premature infants in transit at birth from the placental to the pulmonary type of respiration and the frequency of asphyxial attacks in the neonatal period.

Another striking manifestation of the physiologic immaturity of the premature infant is his erratic control of body temperature. The

TABLE 3.—*Physiologic Basis for Faulty Control of Body Temperature of Premature Infants*

1. A low total heat production dependent on body inactivity and feeble muscular development	
2. A surface area out of proportion to body weight 3. A paucity of insulating subcutaneous fat	Permit excessive loss of heat by radiation and convection
4. Incomplete function of the sweating mechanism when exposed to heat	
5. (Also postulated) inadequate nervous control of vasomotor mechanism	

TABLE 4.—*Total Catabolism of Premature Infants*

Subject	Number of Days	Average Weight, Kg.	Calories per Kg./24 Hr.
C	9	1.8	61
B	24	2.1	70
L	20	2.1	63
O	12	2.1	63
E	9	2.2	73
M	11	2.3	72
C	11	2.4	74
P	9	2.6	65
O	9	2.6	70
L	10	2.7	77
Total	124		
Average		2.3	69 (19% above basal)
Full term			82 (40% above basal)

maintenance of body temperature at a constant level bespeaks a state of equilibrium between production and loss of heat. Any disturbance of this balance must result in pathologic alterations of body temperature. As shown in table 3, the capricious body temperature of the premature infant depends on imperfect regulation of both heat production and heat loss.

The low total heat production common to all premature infants is shown in table 4.[3]

3. Many of the tables and figures in this paper and the succeeding one have appeared in the series entitled "Respiratory Metabolism in Infancy and Childhood," published in this journal.

The total heat available for maintaining body temperature, as estimated for 10 premature infants, averaged 69 calories per kilogram per twenty-four hours, in contrast to the average catabolism of 82 calories per kilogram for the full term infants. The major factor accounting for the lowered catabolism of premature infants is the insignificant amount of heat produced by crying and muscular activity, averaging 10 calories per kilogram per day. This constitutes an increase of only 19 per cent above the basal level, as compared with an average increase of 40 per cent for full term infants. The inactivity of the premature infant during the early part of his postnatal existence

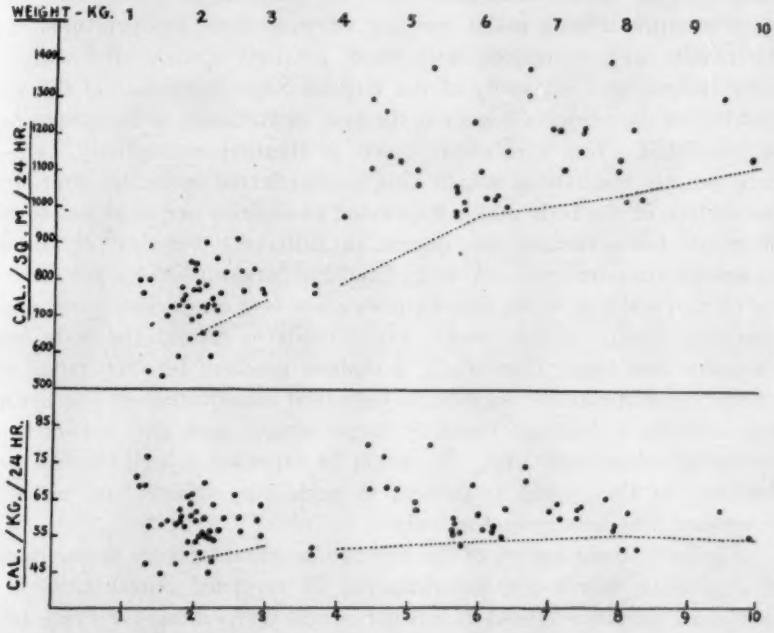

Fig. 5.—Basal heat production of premature and full term infants in terms of weight and of surface area. Each dot denotes a single measurement. The dotted line shows the normal curve.

simulates the behavior of a small hibernating animal, but the animal in nature is ordinarily protected by a fur coat.

Since the rate of heat loss is dependent on body surface rather than on body weight, the already low total heat production per unit of weight gains added significance when calculated in terms of surface area.

Figure 5 compares graphically the basal heat production of premature and of full term infants in terms of body weight and body surface. Each dot denotes a single measurement; the weight range of the infants studied varied from 1.0 to 3.0 Kg. and from 3.5 to 10.0 Kg.

It will be noted that the basal metabolism of both groups of infants (those below and those above 3.0 Kg. in weight) is practically the same per kilogram, but it is considerably lower per square meter of body surface for the group of smaller infants.

The most acceptable explanation for the inherently low rate of total heat production by premature infants is, then, their relatively large surface area and their general inactivity.

These subjects not only produce a low total amount of heat but also tend to lose an excessive amount of heat. The rate of heat loss may be objectively determined by simultaneously measuring rectal and skin temperatures. Such measurements were made by Dr. Richard Day [4] on premature infants under varying environmental temperatures, and the results were compared with those obtained from adults with the same technic by Dr. Hardy of the Russell Sage Institute. If the total heat loss of the subjects is known, the heat conductance of the tissues may be calculated. The term conductance, or thermal conductivity, as used here denotes the rate at which heat is transferred from the interior to the surface of the body and is expressed as calories per hour per square meter of body surface per degree of difference between rectal and cutaneous temperatures. A steep gradient between the temperature of the rectum and that of the skin signifies a low heat conductance and a high insulating ability of the tissues, which tends to protect the body from excessive heat loss. Conversely, a shallow gradient between rectal and cutaneous temperatures signifies a high heat conductance of the tissues, ascribable to a disproportionately large surface area and a paucity of insulating subcutaneous fat. As might be expected, a high thermal conductivity of the tissues is present in premature infants and tends to accelerate heat loss from the body.

Figure 6 shows curves of the average heat conductance of the tissues of 2 men on which are superimposed 21 recorded observations of 9 premature infants exposed to environmental temperatures varying from 26 to 35 C. (79 to 95 F.). It is seen that in 17 of the 21 observations the thermal conductivity of the premature tissues exceeded that of the adult tissues at all levels of room temperature. These observed high levels of conductance are in accord with expectation when one bears in mind the large surface area and the paucity of body fat of these subjects, factors which favor an accelerated loss of heat from the body. It is significant, however, that these premature infants were able to vary their rate of such loss with changing external conditions by vasodilation of their cutaneous capillaries when exposed to hot surroundings and by vasoconstriction when exposed to the cold. In only 3 of 12 observations was the thermal conductance of the tissues above 15

4. Day, R.: Respiratory Metabolism in Infancy and in Childhood: XXVII. The Body Temperature Regulation of Premature Infants, to be published.

calories per square meter per hour at room temperatures below 30 C. (86 F.), whereas in 7 of 9 observations it exceeded this figure at higher temperatures. The ability of premature infants to adapt their vasomotor apparatus to changing external conditions is confirmed by figure 7, which shows the results obtained from the repeated observations of the

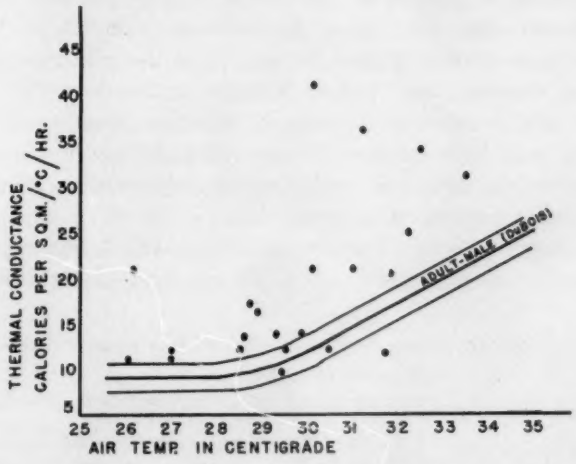

Fig. 6.—Thermal conductance of the tissues of 2 men (solid lines) and of 9 premature infants (21 observations indicated by dots) at room temperatures of 26 to 35 C.

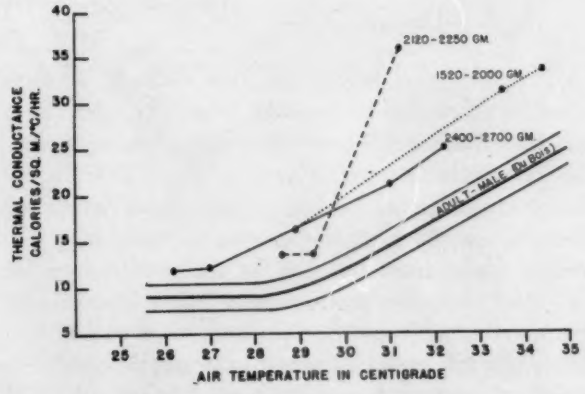

Fig. 7.—Thermal conductance of 3 premature infants showing good vasomotor regulation.

conductance of the tissues of the same infants at different environmental temperatures.

This figure shows the successful response of 3 premature infants whose thermal conductance was studied in repeated observations at

external temperatures ranging from 26 to 35 C. (78.8 to 95 F.). From initial values of 15 calories or less at room temperatures below 29 C. (84.2 F.), they rose to between 25 and 35 calories at the higher temperatures. By constriction and dilation of their cutaneous capillaries in cold and warm environments respectively, they were able to adapt themselves to the changing conditions.

The results of studies of tissue conductance, although as yet too few to be conclusive, suggest that the defect in the regulation of the mechanisms of thermal loss by radiation and convection observed in premature infants is dependent primarily on their large surface area and their paucity of body fat and not on a sluggish vasomotor control of their cutaneous capillaries, a concept which has recently gained favor without adequate experimental support.

The physiologic factors, then, which explain the tendency of premature infants to have hypothermia when exposed to the cold com-

TABLE 5.—*Average Heat Lost in Vaporization During Basal Periods and Periods of Activity*

	Number of Infants	Number of Observations	Number of Periods	Calories Lost in Vaporization: Average, Percentage	Calories Lost in Vaporization: Range, Percentage
Basal	9	42	73	29.6	(24.0-33.6)
Activity *	6	22	29	27.5	(25.2-30.3)
Total	10	48	102	28.8	(24.0-33.6)

* Periods of activity included intervals of sleep.

prise: (1) a low basal metabolism per unit of body surface; (2) a low total catabolism ascribable to muscular inactivity, and (3) an accelerated heat loss by radiation and convection dependent on a high thermal conductivity of the tissues.

The tendency of premature infants to have fever when exposed to hot environments is usually explained as due to inadequate loss of heat in vaporization of water from the skin as the result of an incomplete development of their sweating mechanism. Table 5 shows the contribution which vaporization from the skin and lungs makes to the total heat loss of such subjects under standard calorimetric conditions.

At chamber temperatures ranging between 26 and 29 C. (78.8 and 84.2 F.) and relative humidities between 30 and 60 per cent, the average heat lost in vaporization represented 29 per cent of the total heat produced, the extreme figures for the 10 infants being 24 and 34 per cent. Under the usual conditions of environment, clothing, diet and activity this mechanism of heat loss apparently functions as efficiently in premature infants as in older subjects, as demonstrated in table 6.

The average figure of 29 per cent and the range of 24 to 34 per cent obtained for these subjects closely parallel those obtained for normal infants, children and men, the respective average figures for the latter groups being 27, 25 and 24 per cent of the total caloric expenditure. The range is likewise similar for the different age groups.

When, however, premature infants are exposed to hot surroundings, the similarity of response no longer holds. Dr. Day studied the efficiency of the sweating mechanism of premature infants and of a control group of full term infants when their feet were immersed in hot water under identical experimental conditions. The progressive warming of the bodies of these infants induced by this procedure was electrically recorded by continuous measurements of their rectal temperatures. When a critical threshold of rectal temperature was reached, visible perspiration appeared on the skin of both groups of subjects, but the magnitude of sweating was conspicuously less in the premature infants.

TABLE 6.—*Percentage of Calories Vaporized in Calorimetric Observations (From Infancy to Old Age)*

Subjects	Number	Number of Observations	Age	Calories per Hour, Average	Water, Gm. per Hr., Average	Percentage of Total Calories Vaporized	
						Average	Range
Infants:							
Premature	10	48	3-74 days	6	3	29	24-34
Normal	4	22	2-11 mo.	16	7	27	25-29
Normal children	6	36	6-11 yr.	42	17	25	21-29
Normal men	12	27	20-47 yr.	71	29	24	20-28*

* Soderstrom, G. F., and Du Bois, E. F.: Clinical Calorimetry: XXV. The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch. Int. Med. 19: 981 (May) 1917.

Whereas beads of perspiration were usually visible on the full term infants, sweating was barely perceptible on most of the premature infants. These visual observations were quantitatively confirmed by Vasti tests and by the use of a so-called sweat meter or electric hygrometer which recorded the vapor pressure of the air immediately surrounding the skin. The latter readings were always notably higher in the older infants. These functional studies provide conclusive evidence in support of the a priori expectation that inadequate diffusion of vapor from the skin is the physiologic basis for the tendency of premature infants to have hyperthermia when exposed to hot surroundings (unpublished data).

The diminished diffusion of moisture from the skin of premature infants under stress is reflected in their lowered daily insensible perspiration as revealed in water balance studies. Figure 8 compares the average results for a group of 14 full term infants studied for sixty days and of 10 premature infants studied for forty-three days under comparable environmental and dietary conditions.

The significantly lower level of daily insensible perspiration of the premature infants is noteworthy, the average value being 41 Gm. per kilogram, contrasted with 68 Gm. per kilogram for the full term infants. As previously mentioned, this lower output of water vapor is probably related to diminished sweat gland activity superimposed on a low total heat production and a relatively high heat loss by radiation and convection.

The remaining significant features of the comparison include a reciprocally higher output of urine in the premature group (the respective figures being 81 and 65 Gm. per kilogram); and a threefold increase in water retention (the average being 13 and 4 Gm. per kilogram). When the prior demands on the available water for dissipation of heat

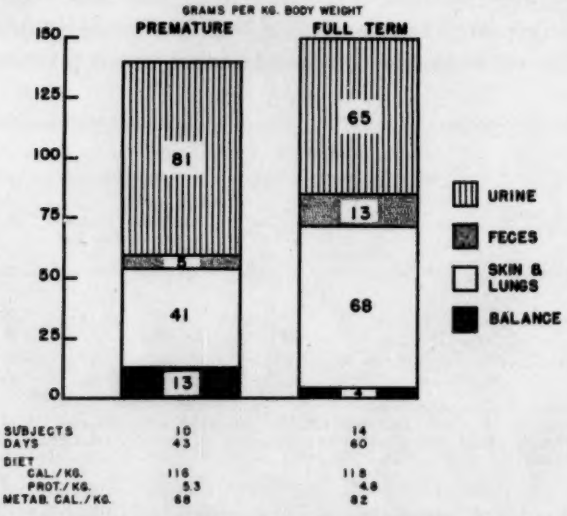

Fig. 8.—Water exchange of premature and of full term infants on adequate diets of cow's milk.

and retention in the body are met, the surplus is excreted in the urine. This surplus, which is seen to be distinctly higher in premature infants than in full term infants on equivalent caloric and fluid intakes, because of their lower extrarenal loss, may serve to compensate for any impairment of renal function, if present. Information is now available indicating that the kidneys of premature infants are less efficient excreting organs than those of full term infants.[5] Measurements have been made of the twenty-four hour urea clearance of 11 premature and 7 full term infants

5. Gordon, H. H.; Harrison, H. E., and McNamara, H.: Urea Clearance of Premature Infants, Am. J. Dis. Child. **62**:894 (Oct.) 1941. Young, W. F.; Hallum, J. L., and McCance, R. A.: The Secretion of Urine by Premature Infants, Arch. Dis. Child. **16**:243 (Dec.) 1941.

less than 2 months of age who were receiving cow's milk formulas of customary fluid intake. The results of 43 observations are presented in figure 9.

A definite correlation is evident between the level of urea clearance in cubic centimeters per square meter per minute and the size of the infants; the smaller the infant, the lower in general was the clearance. As the infants grew older and larger, their values for urea clearance progressively increased, finally reaching the average clearance of 18.5 cc. per square meter per minute obtained in the 7 young full term infants. In only 2 instances was this level attained by infants who weighed less than 2.5 Kg. The improvement in renal function with increasing age and weight is more graphically demonstrated in figure

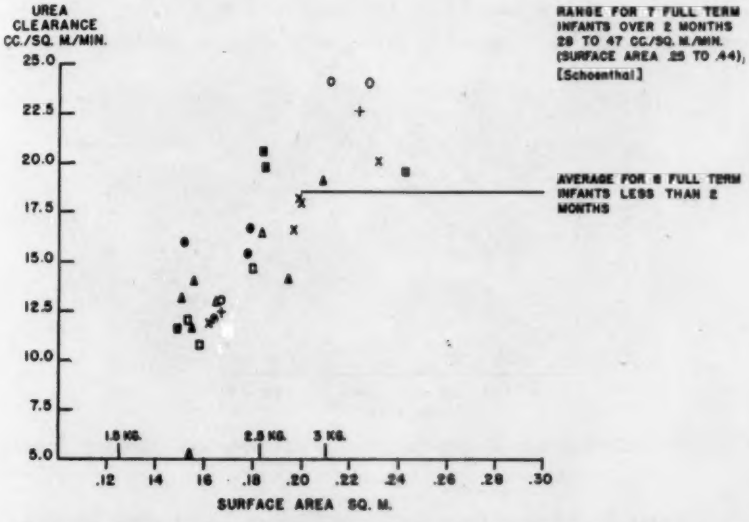

Fig. 9.—Urea clearance of premature infants in relation to the surface area of the body.

10, which shows the results on urea clearance obtained in repeated observations of the same infant.

It is seen that in all 8 of the premature infants there was a striking rise in clearance with increasing age from 5 to 70 days. Intermediate observations on individual infants are not charted, but they reveal that in no instance was a subsequent observation lower than an earlier one.

Whether the observed low values for urea clearance in premature infants are due to a reduced blood flow through the glomeruli and impaired glomerular filtration or excessive renal tubular reabsorption is not yet estabished, and the final answer will require supplementary studies on inulin and diodrast clearances which are now in progress. Two facts, one physiologic and the other morphologic, suggest, however, that a

deficient glomerular filtration is the important pathogenic factor accounting for the impairment. Table 7 shows the results of investigations of urea clearance obtained from 4 premature infants who were studied in repeated observations at two levels of fluid intake, varying from 111 to 218 cc. per kilogram.

Despite a urine flow which increased from 25 to 100 per cent with augmentation of the fluid intake, both the urea in the blood and the clearance remained essentially unchanged at the two levels of flow. Deficient glomerular filtration is also suggested by figure 11, which presents a photomicrograph of the kidney of a full term infant reproduced from an article by M. Clara.[6]

If the decreased patency of the glomerular capillaries and the high columnar epithelium lining the visceral layer of Bowman's capsule,

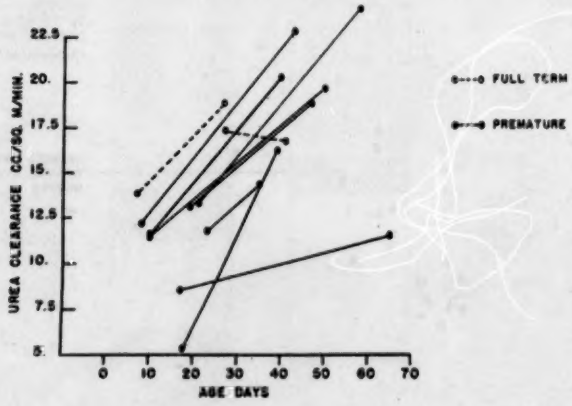

Fig. 10.—Effect of age on urea clearance of full term and premature infants.

TABLE 7.—*Effect of Increased Urine Flow on Twenty-Four Hour Urea Clearance*

Subject	Fluid Intake, Cc./Kg.	Urine, Cc./Min.	Blood Urea Nitrogen, Mg./100 Cc.	Urea Clearance, Cc./Sq. M. per Min.
R. K. 27 days 1.8 Kg.	111	0.05	26	12
	146	0.10	23	12
V. C. 8 days 2.4 Kg.	133	0.14	32	15
	218	0.23	27	15
P. A. 29 days 2.5 Kg.	145	0.20	33	17
	178	0.25	31	18
K. K. 71 days 4.2 Kg.	136	0.14	18	29
	182	0.27	16	31

6. Clara, M.: Vergleichende Histobiologie des Nierenglomerulus und der Lungenalveole, Ztschr. f. mikr.-anat. Forsch. **40**:147, 1936.

which is seen in the peripheral glomerulus, simulate the condition which is present in the premature infant, it is not difficult to envisage an impedance to glomerular filtration. Irrespective of the underlying pathogenesis, it is evident that if the urea clearance is accepted as a valid measure of renal function, the data demonstrate that impairment of this function is another obstacle which the premature infant must hurdle in adapting himself to a changing external environment.

Another important handicap from which the premature infant suffers at birth is the physiologic immaturity of his alimentary apparatus. His digestive tract is called on to ingest, digest and absorb relatively large amounts of food in order to enable him to grow more rapidly than the full term infant who is born with a more efficient digestive apparatus. These heightened demands must be met in the face of weak sucking and swallowing reflexes, a low secretion of gastric hydrochloric acid and digestive enzymes, a faulty absorption of fat and perhaps an incomplete

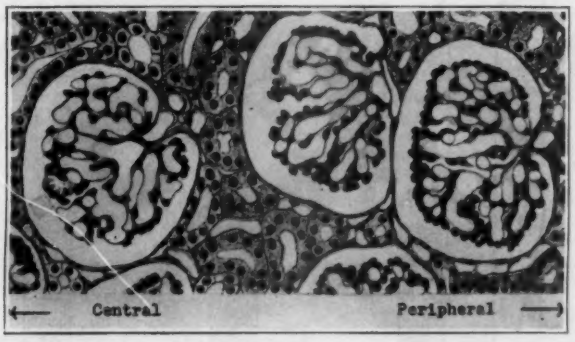

Fig. 11.—Glomerular structure in the kidney of a full term infant (From Clara [6]).

absorption of calcium and other minerals. Little wonder that prematurely born infants are so susceptible to gastrointestinal upsets. The laboratory of the institution with which I am associated has studied in detail only one of the handicaps illustrative of the general immaturity of the alimentary apparatus of the premature infant, his defective absorption of fat.

Comparative studies of fat absorption were made in premature and full term infants [7] receiving isocaloric diets containing equivalent amounts of fat. The results are graphically summarized in figure 12.

Whereas 9 of the 10 full term infants excreted 10 calories or less per kilogram of body weight as fecal fat in twenty-four hours, the

7. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: I. Effect on Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child. **62**:328-345 (Aug.) 1941. McNamara, H., and Gordon, H. H.: Fat Excretion of Premature Infants: II. Effect on Fecal Fat of Quality of Fat Intake, to be published.

fecal fat fell within this range in only 6 of the 31 premature infants studied, the remaining 25 exceeding this value by an appreciable margin. In 9 (29 per cent) of the latter subjects the excretion of fecal fat reached the high level of more than 20 calories per kilogram per day.

It is evident from these and other observations that many premature infants exhibit a defect in their alimentary absorption of fat. The pathogenesis of the defect is, however, not yet established. All that may be said with any assurance at present is that the impairment cannot be explained by a defect of the fat-splitting mechanisms. Table 8 shows the total fecal fat and the percentage excreted as split fat—soaps and free fatty acids—for 4 premature infants in three successive periods during which they received isocaloric diets of similar fat content but differing in the type of fat fed.

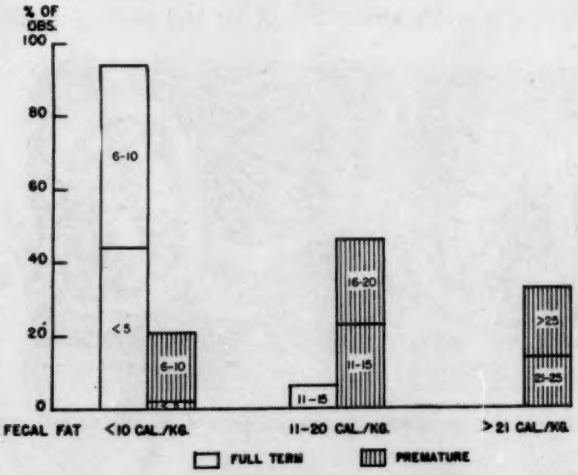

Fig. 12.—Excretion of fat by young full term and premature infants.

TABLE 8.—*Relation of Type of Fat in Diet to Fecal Fat*

Type of Fat in Diet	Fecal Fat		Fecal Fat	
	Gm./Kg.	Percentage as Split Fat	Gm./Kg.	Percentage as Split Fat
	M. S.		B. H.	
Olive oil	2.7	63	2.1	55
Cow's milk	2.6	92	1.9	88
Olive oil	2.6	58	1.3	65
	I. S.		T. M.	
Cow's milk	1.2	93	1.7	93
Olive oil	0.7	67	1.5	56
Cow's milk	1.0	89	1.1	92

M. S. 1.5 to 1.9 Kg. 13 to 32 days; B. H. 1.8 to 2.5 Kg. 16 to 35 days; I. S. 1.8 to 2.4 Kg. 12 to 28 days; T. M. 1.9 to 2.4 Kg. 9 to 25 days

To 2 of the infants, M. S. and B. H., olive oil was fed for a period of seven days, butter fat for the next seven days and olive oil for the last

seven days. To 2 other infants, I. S. and T. M., butter fat was fed for seven days, olive oil for the next seven days and butter fat for the last seven days. It is once more seen that the total fecal fat remains essentially constant in each series of observations, irrespective of the type of fat fed. Of even greater interest is the fact that the degree of fat splitting had no effect on the total excretion, such variations depending entirely on the form of fat in the diet. With the butter fat of cow's milk, the percentage of split fat ranged between the high levels of 88 and 93; with olive oil, the range was at the low level of 55 to 67 per cent. Despite these striking differences in fecal fat partition, the total fat excretion was essentially the same in each series of observations. The conclusion seems valid that ability or inability of the alimentary tract to split fat is not the determining factor in the defective absorption of fat exhibited by premature infants. This conclusion was corroborated by observations of 2 premature infants who were fed on ox bile. This procedure

TABLE 9.—*Factors Contributing to the Anemia of Prematurity*

1. Deficient antenatal storage.....	Iron, copper, other hematogenous factors ?
2. Faulty hemopoiesis.....	Immaturity of centers, faulty hemoglobin synthesis
3. Increased blood destruction.....	Embryonal nature of blood, lowered osmotic resistance of red blood cells
4. Rapid rate of body growth.....	Increased demands
5. Blood dilution.....	Mechanical exaggeration
6. Susceptibility to exogenous factors	Gastrointestinal upsets, parenteral infections, deficiency states

resulted in the expected increase of the ability to split fat but it was entirely without effect on the total output of fecal fat. Whether their defect in the transport of fat across the intestinal wall is dependent on an anatomic underdevelopment of the capillaries and villi, on a functional impairment of the enzyme mechanisms concerned with phosphorylation of fat or on differences of intestinal motility is at present being studied.

Regardless of the exact mechanisms underlying the defect, it is apparent that the failure of some premature infants to thrive on presumably adequate diets may depend on faulty absorption of ingested fat.

The tendency for severe states of hypochromic anemia, hemorrhagic disease and rickets to develop in the premature infant is well known, and the pathogenesis of these handicaps is sufficiently well established to merit only brief discussion.

The chief factors (table 9) contributing to the special susceptibility of premature infants to anemia include: (1) a deficient antenatal storage of iron, copper and perhaps other essential hematogenous factors; (2) faulty hemopoiesis, related probably to the mechanical fac-

tor of a paucity of bone marrow, the functional factor of an immaturity of the hemopoietic centers and perhaps also to an incomplete development of the enzyme systems involved in hemoglobin synthesis; (3) increased destruction of blood, dependent on the more embryonal nature of their blood and the lowered osmotic resistance of erythrocytes (the resulting high level of bilirubinemia is accentuated by the lowered excretory capacity of the immature liver); (4) the rapid rate of body growth, with its increased demands for a high blood balance superimposed on an already poorly functioning blood-forming apparatus; (5) a state of blood dilution, associated with the generally high body hydration of premature infants, which mechanically exaggerates any evidence of an already existent anemia; (6) a heightened susceptibility to exogenous factors, such as gastrointestinal upsets, parenteral infections and deficiency states, which when present tend to aggravate any anemia already existent. The first four items listed in the table are probably primary; the last two, secondary.

TABLE 10.—*Pathogenesis of Hemorrhagic Manifestations*

1. Fragility of capillaries.....	Paucity of elastic tissues Frequency of anoxia Low antenatal storage of vitamin C
2. Hypoprothrombinemia.....	Faulty placental transmission of vitamin K Impaired conversion of vitamin K to prothrombin Increased destruction of prothrombin by lungs

The tendency of the premature infant to have hemorrhagic manifestations (table 10) of a serious nature is also readily explained by the extreme fragility of his capillaries and the low prothrombin content of his blood plasma, the level in the neonatal period sometimes being as low as 5 per cent of the adult value. The paucity of vascular elastic tissue, the frequent occurrence of anoxia, with its deleterious effect on capillary integrity, and the low body reserves of vitamin C required for building so-called cementing substance are probably the chief factors contributing to the increased permeability of the capillaries of the premature infant. Whether the low levels, or more accurately the marked fluctuations, of plasma prothrombin are due to a faulty placental transmission of vitamin K, to impaired conversion of the vitamin to prothrombin incident to hepatic immaturity or to increased destruction of prothrombin by the lungs and other organs remains as yet unsettled.

The heightened susceptibility of premature infants to infections is probably related to a number of factors, among which the most important appear to be: (1) a deficient placental transmission of immune substances; (2) defective formation of granulocytes in bone marrow; (3) increased body hydration, and (4) impaired capacity of the premature organism to manufacture immune substances, probably

dependent on incomplete development of enzyme systems and hepatic immaturity with faulty globulin synthesis.

A reduced antenatal storage of calcium, phosphorus and possibly vitamin D predisposes the premature infant to rickets (table 11). This inherent predisposition is aggravated by a number of contributing factors: a decreased gastrointestinal tolerance of fat and presumably of the fat-soluble vitamins; the rapid rate of body growth and consequent increased demands of the body for retention of calcium and phosphorus for skeletal accretion, often in the face of a diminished dietary supply provided in human milk; and the necessity for remaining indoors and away from the sun for a longer time than is necessary for the full term infant. Even if vitamin D is administered and shown to be absorbed in adequate amounts, its efficacy in promoting renal tubular reabsorption of phosphate, which Dr. Harrison [8] has demonstrated to be one of the functions of this vitamin in older subjects, may be minimal

TABLE 11.—*Factors Contributing to Rickets*

1. Reduced antenatal storage.....	Calcium Phosphorus Vitamin D ?
2. Defect in alimentary absorption.....	Fat Fat soluble vitamins Minerals ?
3. Rapid body growth.....	Increased demands
4. Diminished mineral intake.....	In human milk
5. Life indoors and away from sun.....	Lack of vitamin D
6. Impaired renal absorption of phosphate ?	

as a result of the previously shown defect in renal function exhibited by the premature infant. This impairment, if present, together with faulty alimentary absorption of vitamin D may explain the high dosage of the vitamin needed to prevent rickets in these subjects.

It is of interest in this connection to mention that Dr. Helen Benjamin [9] found that faulty absorption of calcium and phosphorus from the gastrointestinal tract of premature infants cannot be considered an important contributory factor. She found no evidence of defective absorption or increased reexcretion of calcium in balance studies and further showed that augmentation of the intake was accompanied by practically quantitative absorption of the extra calcium ingested.

Although the pronounced susceptibility of premature infants to vitamin D deficiency has long been known, only recently has the important role of vitamin C in his nutrition been demonstrated.

8. Harrison, H. E., and Harrison, H. C.: Renal Excretion of Inorganic Phosphate in Relation to Action of Vitamin D and Parathyroid Hormone, J. Clin. Investigation **20**:47-55 (Jan.) 1941.

9. Benjamin, H. R.; Gordon, H. H., and Marples, E.: The Calcium and Phosphorus Requirements of Premature Infants (in preparation).

In a study of the creatinuria of premature infants, it was discovered [10] that practically all of the infants who were fed relatively high protein diets of preheated cow's milk without added supplements of vitamin C excreted chromogenic substances in their urine which gave the Jaffé reaction but which proved not to be creatinine. These abnormal urinary products were isolated and identified chemically by Dr. Hans Clarke and spectroscopically by Dr. Konrad Dobriner as l-parahydroxyphenyllactic and parahydroxyphenylpyruvic acids, intermediary metabolites of the aromatic amino acids tyrosine and phenylalanine. More recently it has been found that augmentation of the intake of these amino acids by their ingestion in pure form also leads to the appearance in the urine of the amino acids themselves and of phenlypyruvic acid.

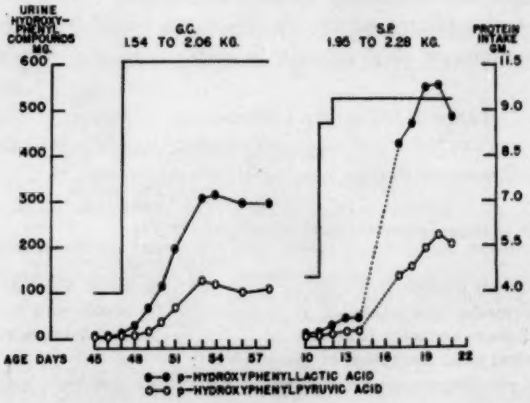

Fig. 13.—Urinary excretion of parahydroxyphenyllactic acid and parahydroxyphenylpyruvic acid of 2 premature infants changed from a diet of human milk to a diet of cow's milk.

Typical examples of this aberration in aromatic amino acid metabolism in premature infants fed cow's milk are illustrated in figure 13. Intermediary metabolites were absent from the urine in these 2 infants while on diets of human milk containing approximately 4 Gm. of total protein, or 2.5 Gm. per kilogram, per day. Following a twofold increase on the cow's milk diets to more than 10 Gm. of protein daily, or about 6 Gm. per kilogram, the urinary excretion of both parahydroxyphenyllactic and parahydroxyphenylpyruvic acid began to rise, reaching a

10. Levine, S. Z.; Marples, E., and Gordon, H. H.: Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: I. Identification and Assay of Intermediary Products, J. Clin. Investigation **20**:199-207 (March) 1941. Levine, S. Z.; Gordon, H. H., and Marples, E.: Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, ibid. **20**:209-219 (March) 1941.

maximum on or about the seventh day of the high protein diets and remaining at this peak for as long as observations were continued.

Figure 14 shows even more graphically the dependence of the defect on the level of aromatic amino acid intake. The premature infant for whom data are presented was fed human and cow's milk of varying protein content and correspondingly varying intakes of phenylalanine and tyrosine in successive experimental periods. A striking parallelism is noted between the intake of these aromatic amino acids expressed as tyrosine and the urinary output of hydroxyphenyl compounds, also expressed as tyrosine, the level of output being directly proportional to the level of intake in the different periods.

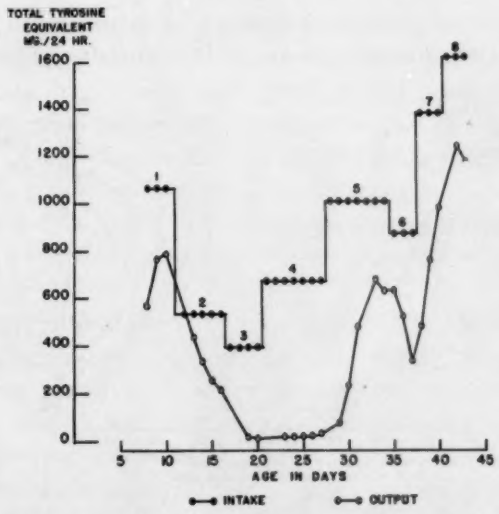

Fig. 14.—Intake and output of phenylalanine and tyrosine (expressed as tyrosine) of a premature infant.

Without exception, the parenteral or oral administration of vitamin C in single or divided doses totaling 100 to 500 mg. of l-ascorbic acid resulted in the prompt eradication of abnormal metabolites from the urine.

Figure 15 illustrates the typical effect of this vitamin on the metabolic aberration. The injection of 50 mg. of l-ascorbic acid was without significant effect on the urinary excretion of the aromatic keto and oxy acids. Following an increased dose of 100 mg. two days later, a prompt decline occurred within twenty-four hours, with practical disappearance of both products in forty-eight hours. When the effect of vitamin C had worn off, the keto and oxy acids gradually reappeared in the urine, eventually reaching even higher levels than in the first control period. Two injections of ascorbic acid, each of 200 mg., again resulted in a dramatic abolition of the defect within forty-eight hours. It may be

definitely stated that the defect in aromatic amino acid metabolism can be produced at will in premature infants by feeding them cow's milk mixtures containing 5 Gm. or more of milk proteins per kilogram and by withholding vitamin C and that it can be promptly eradicated by the oral or parenteral administration of this vitamin in adequate dosage.

This action of vitamin C is apparently specific, since no other substances yet tried have consistently abolished the defect. These have included vitamins A and D, thiamine hydrochloride, riboflavin, niacin (nicotinic acid), pyridoxine (vitamin B_6), biotin, pantothenic acid, choline chloride, rice polishings, powdered yeast, crude liver extract and alpha tocopherol, given singly or in combination and in maximal dosage for several days.

The demonstration of the important role of vitamin C in completing the oxidation of the aromatic amino acids phenylalanine and tyrosine

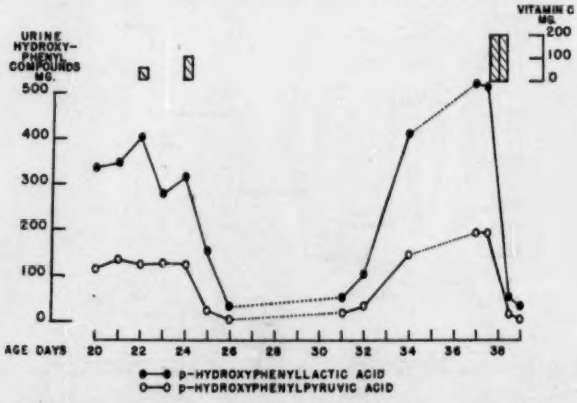

Fig. 15.—Effect of administration of vitamin C on the urinary excretion of hydroxyphenyl compounds.

gives rise to a number of intriguing but as yet highly conjectural questions. Since tyrosine is a precursor of the calorifacient hormones thyroxin and epinephrine, may the presence of the defect in premature infants contribute under certain conditions to their instability of body temperature regulation? Is the delicate transparency of the skin of premature infants related to improper utilization of melanin, another product of tyrosine? Does the observed increased excretion of aromatic organic acids in premature infants fed cow's milk play a contributory role in their known tendency to have severe rickets? Many other questions arise, but they are all matters of surmise at present and must await further study. The observations, however, do establish from a practical point of view the importance of giving vitamin C in large dosage soon after birth to all premature infants, particularly if they are on diets of cow's milk.

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PHYSIOLOGIC HANDICAPS OF THE PREMATURE INFANT

II. CLINICAL APPLICATIONS

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In this portion of the review, consideration will be given to some important clinical measures which have proved their usefulness in combating the inordinately high death rate of premature infants, especially in the neonatal period. Because the health of the mother and conditions in utero and at delivery are reflected in the well-being of the offspring, a proper supervisory program for the health of premature infants necessarily begins in the antenatal and intranatal periods. Table 1 contains a list of suggested measures designed to lower the mortality of premature infants.

These so-called obstetric aids are separated in the table into general prophylactic measures which may be taken during pregnancy to prolong the gestation period of the fetus in utero and specific preventive and therapeutic procedures which may aid in combating some of the commonly impending symptoms.

The general measures include institution of an antepartum program of diet, hygiene and general care designed to promote an optimal state of maternal health, and provision for proper medical attention to all complications of pregnancy which may occur. There is no need to discuss the first point at length. It is self-evident that conditions, such as improper diet, which impair the health of the mother, overwork and worry with consequent exhaustion, accidents, improper spacing of pregnancies and overindulgence in sexual intercourse late in pregnancy may precipitate the occurrence of or accentuate an already existent tendency to premature birth. It is also evident that gestation may be prolonged and premature births postponed by prompt and adequate treatment of pregnant women who are suffering from heart disease, thyroid disorders, diabetes mellitus, syphilis, pyelitis, anemia and other

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Benjamin Knox Rachford Lecture, delivered by S. Z. Levine at Cincinnati, Oct. 24, 1941.

From the Department of Pediatrics, Cornell University Medical College, and the New York Hospital.

complications. The value of chemotherapy in infections and the possible use of vitamin E in prolonging gestation should also be mentioned.

Among the specific measures are included procedures which tend to minimize the severity of such potentially impending symptoms as asphyxia, hemorrhage, anemia, birth trauma, hypothermia and infections. The incidence of cyanotic attacks may be reduced by abstaining from the use of narcotics and analgesics shortly before and at delivery; by gentle manipulation during the actual delivery; by removal of foreign material from the respiratory passages of the infant after birth, and by the use of stimulants and oxygen when indicated. The tendency to hemorrhage may be counteracted by incorporating adequate amounts of vitamin C in the maternal diet throughout pregnancy; by administra-

TABLE 1.—*Obstetric Aids Aimed at Lowering the Mortality of Premature Infants*

General measures to prolong the period of gestation	
Promotion of optimal maternal health	
Treatment of complications of pregnancy	
Specific measures to mitigate common symptoms	
Asphyxia	**Avoidance of narcotics and anesthetics**
	Gentle manipulations at delivery
	Suction of respiratory tract at birth
	Administration of stimulants and oxygen at birth
Hemorrhage	**Adequate vitamin C in maternal diet**
	Vitamin K prior to or after delivery
	Transfusions at birth
Anemia	**Adequate maternal diet**
	Delay in severance of umbilical cord
	Transfusions at birth
Trauma	**Gentle manipulations at delivery**
	Avoidance of operative procedures
Hypothermia	**Avoidance of chilling at birth**
Infections	**Separate unit space**

tion of vitamin K to the mother prior to, or to the infant immediately after, delivery, and, if necessary, by transfusions at birth. Although the anemia of prematurity cannot be wholly prevented by prenatal and intranatal measures, its severity may be mitigated by an adequate maternal diet, by delay in severance of the umbilical cord at delivery until pulsations have ceased and by transfusions at birth and in the neonatal period. The frequency of birth trauma may be combated by gentle handling at delivery, with avoidance when possible of anesthesia and operative procedures. Chilling must be rigorously avoided at and after birth. The attempt to build up the resistance of the premature infant to infections belongs more properly to postnatal care, but separate unit space should be at hand to receive the baby at birth.

It is, of course, needless to add that besides the specific measures recorded as aids in combating particular symptoms, all general measures

which delay premature birth serve the same purpose, by promoting the maturity of the organism and by enhancing the placental transmission and antenatal storage of essential elements. This paper, however, deals chiefly with the therapeutic procedures which the pediatrician may take in early postnatal life to meet effectively the anticipated contingencies and frequent emergencies encountered by the premature infant.

It has been reiterated time and again that the four cardinal points of good postnatal care of the premature infant comprise control of body temperature, prevention of infections, skilled medical and nursing supervision and proper feeding. Preparedness for immediate emergency treatment is also an essential component. These elements are arranged in tabular form in table 2.

TABLE 2.—*Essentials of Good Postnatal Care of Premature Infants*

1. Preparation for birth of infant	External heat Provisions for resuscitation Skilled personnel
2. Facilities for transfer of infants	External heat
3. Premature accommodations	Unit space
Personnel.....	Medical supervision Skilled nursing service
Facilities.....	Space, air, light, temperature, ventilation, hot and cold running water, provisions for isolation
Equipment (individualized).	Segregation of supplies, scale, provisions for suction, oxygen, transfusions, etc.
Care (aseptic technic).....	Examinations, visitors, milk room, baths, records of temperature, weight, stools, abnormal symptoms, diagnostic and therapeutic management
4. Feeding	
5. Preparations for discharge	
Maternal instruction.....	Breast milk supply, care of infant
Appraisal of home.....	Bed, room, food, utensils
Continuing medical care.....	Follow-up clinic

Application of these principles of management may best be illustrated by a review of the detailed handling of a premature infant from the moment of birth to the end of the first half year.

REPORT OF HANDLING OF INFANT

The infant whose record is graphically presented on the chart (fig. 1) was born after six months' gestation on April 16, 1941 in the obstetric delivery room of the New York Hospital. The mother was a Negro primipara who had been followed in the antepartum clinic. Her health was good and the pregnancy uncomplicated until the birth of the infant was precipitated by a premature rupture of the membranes. In preparation for the expected arrival of a small, immature baby, a pediatrician had been summoned to the delivery room; the temperature of the receiving bed had been elevated, and warm, sterile blankets were on hand to receive the infant. The delivery of the infant was spontaneous and gently managed without resort to narcotics and anesthetics, and the umbilical cord was not cut until all pulsations had ceased. The child, a girl, weighed 662 Gm. (1 pound 7 ounces). She was

immediately wrapped in the prepared blankets; a large amount of bloody mucus which seeped from the nose and mouth was gently aspirated by suction with a soft rubber catheter, and oxygen was administered by mask. Despite the apparently hopeless prognosis, these emergency measures were instituted in the delivery room under skilled medical supervision in an effort to forestall birth trauma, chilling and exposure, the occurrence of atelectasis and aspiration pneumonia and the anticipated anemia.

The infant was then put in a heated crib on wheels, equipped with a portable device for administering oxygen by mask, and immediately transferred to one of

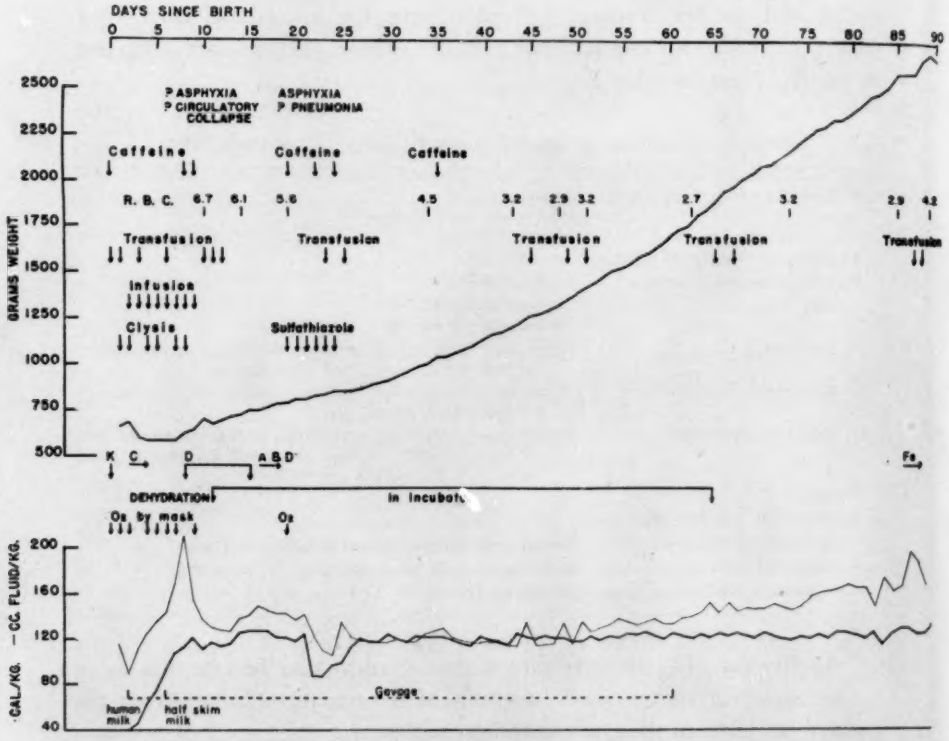

Fig. 1.—Clinical record of a premature infant graphically presented.

the air-conditioned premature nurseries of the pediatric department. The temperature of this seven bed room is constantly maintained at 77 F., and the relative humidity is kept at 65 per cent. Since these external conditions were obviously not optimal for this tiny baby, supplemental heat was immediately applied by means of hot water bottles and a heated cradle. The initial rectal temperature of 34.4 C. (93.9 F.) gradually rose with this external heat to 37 C. (98.6 F.). Three of the trained nurses on duty in the unit were assigned to the sole care of the infant throughout the twenty-four hours of the day and night.

Four hours after her admission to the premature unit and after her rectal temperature had reached a relatively normal level, she was rapidly examined with a minimum of exposure to determine her viability and the presence of congenital

anomalies. During the examination her color became dusky and the respirations gasping. Stimulants in the form of epinephrine (0.2 cc. of a 1:1,000 solution of epinephrine hydrochloride) and caffeine with sodium benzoate (0.06 Gm.) were parenterally administered; suction was gently applied to the upper respiratory tract; oxygen was given continuously by mask, and subsequently 2 mg. of synthetic vitamin K (menadione) was injected and an intravenous transfusion of 15 cc. of banked blood given.

For the first three weeks the infant had frequent recurrences of asphyxial attacks and circulatory collapse, manifested by deep cyanosis and cold, blue extremities. These symptoms were treated by repeated suction and removal of mucus from the upper portion of the respiratory tract, intermittent use of caffeine and continuous administration of oxygen. The tendency to hemorrhage, as manifested by the presence of blood in the nasal and oral secretions, was, as previously stated, treated by the immediate injection of vitamin K, daily parenteral administration of vitamin C as 25 mg. of ascorbic acid and frequent intravenous transfusions.

Because of weak sucking, gag and cough reflexes and to avoid the danger of aspiration pneumonia, nothing was offered by mouth for the first forty-eight hours. Ordinarily feeding by mouth is begun for heavier premature babies at the end of twelve hours. The fluid requirements during this early postnatal period were maintained by repeated parenteral administrations of transfusions of blood, hypodermoclyses of physiologic solution of sodium chloride and intravenous infusions of 5 per cent dextrose solution. The administration of water by mouth was begun on the second day, in amounts of 5 cc. every three hours by gavage. It will be noted that only on the seventh and eighth day of life did the total fluid intake inadvertently exceed 160 cc. per kilogram of body weight. In accord with expectation, the infant initially lost weight and by the fourth day reached a minimum weight of 588 Gm. (a little less than 1 pound 5 ounces). The body weight remained at this minimal level for three days, and symptoms of dehydration became manifest and persisted despite the previously mentioned high intakes of fluid on the seventh and eighth days. It was then assumed that the persistent dehydration was the result of excessive loss of moisture from the skin arising from exposure to dry external heat in the effort to stabilize the body temperature. On the eleventh day the infant was placed in a self-contained incubator of the Davidson type, in which the temperature was maintained between 85 and 90 F. and the relative humidity at the constant high level of 65 to 70 per cent. She remained in the incubator until the sixty-fifth day of life with no recurrence of dehydration and with a normal body temperature. During the early part of her stay in the incubator, the oxygen content of the surrounding air was maintained at around 40 per cent by the continuous admission of oxygen to combat the persistent atelectasis which was present. As frequently happens, signs of pulmonary consolidation of infectious or aspiratory origin developed and required the transient use of sulfathiazole.

The tendency to rickets and osteoporosis was combated by the addition to her diet on the eighth day of a water-soluble vitamin D concentrate (drisdol) and on the sixteenth day of vitamin A, as well as by the early replacement, on the sixth day, of human milk by a cow's milk mixture of high mineral content. Administration of both vitamins in large doses was continued throughout her stay in the hospital.

Despite the delay in severance of the umbilical cord at birth and the frequent transfusions in the early course of her existence, the infant showed a progressive fall in hemoglobin content, and the red blood cell count dropped from initial levels

of above 6,000,000 to as low as 2,700,000 on the sixty-second day of life. The tendency of premature infants to have severe hypochromic anemia was exemplified by this infant. Her anemia has persisted to the time of writing this report, even though she continued to receive intermittent transfusions, which were supplemented by the administration of medicinal iron eighty-six days after birth. When seen at the age of 5 months, her hemoglobin content was still only 10.5 Gm. At 6 months it had risen to 12.5 Gm. These observations are in accord with the concept that the anemia of prematurity is dependent on a faulty hemopoietic function, apart from increased blood destruction and other factors.

The methods employed for feeding the infant are of special interest. In the first place, it will be seen from figure 1 that for the first sixty-one days of life she was fed entirely by gavage, without manifest signs of irritation to her upper respiratory tract or to her alimentary passages. This prolonged period of gavage feeding was employed because her sucking reflexes and muscles of deglutition were not sufficiently developed to permit spontaneous oral feeding without inducing exhaustion and because the presence of weak gag and cough reflexes presented the constant danger of aspiration of food into the respiratory passages. It will be further noted that after the perilous early postnatal period the infant gained weight steadily; when she was discharged from the hospital on the ninetieth day her weight was 2,660 Gm. (5 pounds 14 ounces), an average daily rate of gain of 22 Gm., or nearly 1 ounce. At no time throughout this entire period was she fed a diet containing more than 120 calories per kilogram of body weight, an amount which is below that customarily fed to premature infants. Furthermore, this level of oral caloric intake was reached only on the ninth day of postnatal life, again to obviate potential respiratory and alimentary complications. The fluid intake was maintained at a correspondingly low level, exceeding 160 cc. per kilogram of body weight only on the seventh and eighth days and after eighty days, the range of intake during the intervening period falling between 120 and 140 cc. per kilogram. Finally, attention is called to the early replacement of human milk by a half skimmed cow's milk mixture (alacta) on the sixth day of life.

COMMENT

The reasons for using this type of feeding merit comment. The basis for employing a diet low in calories in shown in table 3, which lists the daily caloric requirements of 33 premature infants as determined by metabolic measurement.

Their basal needs were covered by an average of 60 calories per kilogram per day, the range being from 50 to 75 calories per kilogram. The small quota of 10 calories per kilogram allocated to specific dynamic action and activity is readily explained by the small amounts of food which they routinely ingest and by their feeble movements. To this average total catabolic requirement must be added the high average figure of 20 calories per kilogram to cover the caloric loss in the feces, chiefly as fecal fat. Most premature infants can therefore maintain their weight on daily diets containing 90 calories with an upper value rarely exceeding 100 calories per kilogram. The caloric needs for body growth are not established with the same degree of certainty. If, however, one is willing to accept the reasonable premise that the average

daily rate of gain in weight of 12 Gm. per kilogram which takes place in the last intrauterine month constitutes an adequate rate of gain in the early postnatal period, it may be estimated that an increment of 30 calories, or 2.5 calories per gram of expected weight gain, in the intake is sufficient to cover the anabolic needs of premature infants. A total, then, of 120 calories per kilogram in the daily diet, particularly if a cow's milk mixture low in fat is used, is adequate to cover the total caloric needs of most premature infants.

The validity of applying these experimental observations to actual practice has been fully confirmed by analysis of the weight gains of premature infants born in the clinic of the institution with which I am associated. Their rate of gain was wholly satisfactory on diets which rarely exceeded this figure of 120 calories per kilogram. On purely

TABLE 3.—*Approximate Caloric Requirements of Premature Infants*

	Calories per Kg./24 Hr.	
	Mean	Range
Basal	60	50 to 75*
Specific dynamic action activity	10	
Total catabolism	70	60 to 75†
Feces	20	10 to 30
Maintenance	90	75 to 100
Gain in weight	30	25 to 35‡
Total	120	100 to 135

* Twenty-two infants.
† Eleven additional infants.
‡ Rate of weight gain in utero, grams × 2.5 calories.

theoretic grounds also, this use of low caloric diets is preferable. Because of weak sucking reflexes, easy fatigability, poor gag and cough reflexes and the readiness with which respiratory embarrassment, abdominal distention and diarrhea may be produced in premature infants, it is obviously better practice to feed the minimum amount of food and fluid which will result in satisfactory weight gains than the maximum amounts which the patients can tolerate.

The indications for feeding premature infants diets low in fat were described in paper I of this review. Table 4 illustrates the beneficial effect on the alimentary absorption of fat of reducing the amount of fat in the diet. In two control periods totaling eighteen days during which 1 premature infant was fed a half-skimmed cow's milk mixture containing less than 2 Gm. of fat per kilogram, the fecal fat averaged less than 1 Gm. per kilogram per day, and the infant gained approximately 15 Gm. of weight daily. When the dietary fat was raised in a subsequent period of one week to 4.4 Gm. per kilogram without changing the total dietary calories, the fecal fat rose to 1.9 Gm. per kilogram, a

twofold increase above the control levels, and the daily gain in body weight correspondingly fell to 7 Gm. Resumption of the control diet of low fat content was again accompanied by a decreased loss of fat and an increased increment of weight. The response of the second infant to similar changes in the fat content of the diet paralleled, and was perhaps even more striking than, that of the first infant, the fecal fat rising threefold above the control levels in the seven day period of high fat intake.

TABLE 4.—*Effect of Varying the Amount of Dietary Fat on Excretion of Fat*

Infant	Days	Dietary Fat, Gm./Kg.	Fecal Fat		Weight Gain, Gm./Kg.
			Gm./Kg.	Percentage of Dietary Calories	
				98 to 105 calories per Kg. in diet	
P. A.	10	1.7	1.0	9	14
	8	1.8	0.8	7	15
	7	4.4	1.9	17	7
	9	2.0	0.7	7	16
				104 to 107 calories per Kg. in diet	
H. A.	11	2.1	1.2	10	13
	8	2.0	1.1	10	15
	7	3.9	3.3	30	5
	9	2.0	0.7	6	14

TABLE 5.—*Absorption of Nitrogen by Premature Infants* *

Type of Milk	Number of Observations	Number of Days	Average Protein Intake, Gm./Kg./24 Hr.	Coefficient of Digestibility, per Cent †
Cow's	5	25	2.8	88 (84-92)
Cow's	6	31	4.8	91 (87-94)
Cow's	1	4	9.1	93

* Average age 33 to 40 days, average weight 2.1 to 2.6 Kg.

† $\frac{\text{Dietary nitrogen} - \text{fecal nitrogen}}{\text{Dietary nitrogen}} \times 100.$

Because of the failure of some premature infants to thrive on presumably adequate diets containing 120 calories per kilogram as the result of faulty absorption of ingested fat, it would seem a wiser procedure in such instances to decrease the amount of fat in the diet and to maintain the total dietary calories at the same level by replacement with protein and carbohydrate rather than to follow the usual custom of raising the total calories and perhaps precipitate a digestive upset in an infant who is already handicapped by a low gastrointestinal tolerance.

The validity of substituting protein and carbohydrate for dietary fat is supported by the results of studies on nitrogen absorption and respiratory quotients of premature infants (table 5).

These subjects were found to absorb an average of 88 per cent of the protein in their diets of cow's milk when the daily intake averaged 2.8 Gm. per kilogram of body weight. Augmentation of the intake of cow's milk protein to levels of 4.8 and 9.1 Gm. per kilogram was accompanied by similar and even higher absorption rates, the figures being 91 and 93 per cent at the two levels of dietary protein. These absorption rates compare favorably with those obtained in full term infants. Thus, with the defect in alimentary absorption of fat exhibited by premature infants, there obviously is not a similar defect in absorption of nitrogen.

The studies of the respiratory quotients of premature infants, summarized in table 6, prove that these subjects are capable, even at a very early age, of utilizing carbohydrate as efficiently as full term infants. The average levels of the quotients, 0.88 and higher, obtained in 56 observations on 21 infants 10 of whom were less than 9 days old indicate that prematurity per se does not interfere with the mechanisms concerned with carbohydrate metabolism. Replacement of dietary fat by

TABLE 6.—*Average Respiratory Quotients*

Age of Infants	Number of Infants	Number of Observations	Respiratory Quotients	
			Average	Range
Less than 9 days	10	18	0.88	0.77-0.95
More than 9 days	16	38	0.91	0.87-0.95
Total	21	56	0.90	0.77-0.95

protein and carbohydrate would therefore appear to be a reasonable procedure for premature infants who do not gain weight on customary diets of human milk or mixtures of whole cow's milk.

The routine use of relatively low fluid intakes, of between 130 and 150 cc. per kilogram, in the feeding of premature infants is explained by figure 2. This figure portrays the average results obtained in water balance studies of 15 premature infants for fifty-eight days with four different levels of fluid intake from 74 to 167 cc. per kilogram. It will be seen that with intakes below 95 cc. per kilogram insufficient water was available in the diet to cover the metabolic needs of the infants and large amounts of water were withdrawn from the body, the net result being a negative water balance and the development of dehydration fever. Of greater significance for the present purposes are the results obtained with the higher fluid intakes above these minimal levels. Whether the average fluid content of the diet was as low as 124 or as high as 167 cc. per kilogram, the positive water balances which resulted were essentially of the same order of magnitude. These infants retained in their bodies average daily amounts of water totaling between 19

and 24 Gm., the extra water of the higher intakes merely being eliminated as extra urine. On the basis of these experimental observations and in conformity with the previously enunciated thesis that it is better practice to feed minimal amounts consistent with satisfactory progress, it has been the custom of my associates and me to offer premature infants milk mixtures rarely if ever exceeding 150 or 160 cc. of fluid per kilogram per day.

That the feeding of milk mixtures containing 120 calories per kilogram, 150 cc. of fluid, not more than 2.5 Gm. of fat per kilogram and relatively large amounts of carbohydrate (18 Gm.) and protein (6 Gm.) is compatible with optimal growth in premature infants is demonstrated in the next table.

Table 7 shows the relation of the retention of body water to total body weight gain in 10 premature infants, 4 of whom were studied on

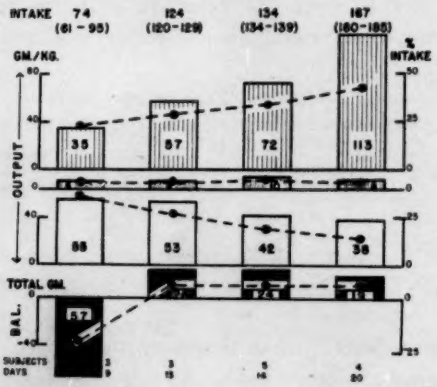

Fig. 2.—Average water balance of 15 premature infants at four levels of intake of water.

human milk and 6 on cow's milk diets for fifty-one days. With both types of diet it is seen that of the total daily gain in weight of 25 to 44 Gm. an average of from 63 to 66 per cent was in the form of body water. Furthermore, the average daily gain was satisfactory in all observations, ranging from 19 to 65 Gm. with the cow's milk feedings, with between 54 and 70 per cent of the water retained as body water. This demonstration that the proportion of retained water to the total increase of weight coincides with the water content of the infantile body, as analyzed chemically, provides experimental evidence that the relative and absolute amounts of organic materials and water deposited in the body on the routine diets previously described are qualitatively and quantitatively compatible with satisfactory growth in premature infants.

One final point should be reiterated in connection with the feeding to premature infants of cow's milk mixtures of low fat and high protein

content. Attention was called in paper I of this study to the increased requirements of these subjects for vitamin C when ingesting diets high in protein. This close interdependence between protein intake and vitamin C has been further established by studies recently completed by Dr. Margaret Dann in our clinic. Using the response of the ascorbic acid of the blood plasma to a test dose of the vitamin as an index of the degree of saturation of the tissues, she made observations on premature infants receiving routine diets of boiled human milk and boiled cow's milk mixtures (table 8).

Each of the 22 infants, 11 in each group, was given a series of large saturation doses of ascorbic acid, totaling 800 or 900 mg., over a four

TABLE 7.—*Relation of Water Retention to Change of Body Weight*

Subject	Days Observed	Intake per Kilogram			Water Retention, Gm.	Body Weight Change, Gm.	Water : Weight, Percentage
		Calories	Protein, Gm.	Water, Gm.			
Human Milk							
R. L.	3	141	2.1	182	13	20	65
N. O.	6	118	2.9	149	20	30	67
E. C.	3	126	1.9	158	15	22	68
E. M.	3	102	4.5	135	19	29	65
Average (4)	15	122	2.9	156	17	25	68
Cow's Milk							
N. O.	3	108	2.5	166	12	19	63
E. M.	3	120	4.8	136	23	33	70
L. O.	12	119	4.2	150	24	45	54
E. O.	4	124	6.0	130	41	65	63
H. L.	12	133	6.1	126	24	42	57
R. L.	2	134	6.3	160	43	61	70
Average (6)	36	123	5.0	145	28	44	63

or a five day period. An interval of six or seven days was allowed to elapse without vitamin C supplement, and then each infant received a test dose of either 100 or 200 mg. of ascorbic acid by mouth or parenterally. Four hours after the test dose the plasma ascorbic acid level was measured. It will be seen that the levels of the group of infants receiving the human milk with a protein intake of between 2.6 and 2.8 Gm. per kilogram were consistently and strikingly higher than the levels in the group fed cow's milk containing from 4.6 to 6.1 Gm. of protein per kilogram. The respective averages were 1.9 and 0.8 mg. per hundred cubic centimeters of blood plasma, and the ranges were from 1.3 to 3.5 mg. and from 0.1 to 1.6 mg. for the two groups of infants. Since both types of diets were of similar caloric content and free from vitamin C, the main difference being that the cow's milk con-

tained twice as much protein as the human milk, the results may be interpreted as signifying that the participation of vitamin C in the intermediary metabolism of protein leads to a more rapid depletion of the stores of the vitamin in the body and that an increased daily supply of the vitamin is necessary when premature infants are fed cow's milk mixtures of high protein content. It is our custom, therefore, to give vitamin C (25 to 50 mg. of ascorbic acid daily) to all premature infants

TABLE 8.—*Storage of Ascorbic Acid* in Premature Infants on Different Intakes of Protein*

Subject †	Protein Average, Gm./Kg./Day	Test Dose,‡ Mg.	Plasma Ascorbic Acid, Mg./100 Cc. 4 Hr. After Test Dose
On Human Milk (Vitamin C-Free)			
1	2.6	100	1.6
2	2.7	100	1.3
3	2.7	100	1.7
4	2.7	100	3.5
5	2.8	200	2.6
6	2.7	200	1.4
7	2.7	200	1.8
8	2.7	200	1.5
9	2.6	200	1.9
10	2.7	200	2.0
11	2.6	200	1.9
			Average 1.9
On Cow's Milk			
1	5.9	100	0.5
2	5.0	100	1.0
3	4.6	100	1.4
4	4.7	200	1.2
5	6.1	200	0.6
6	4.8	200	0.3
7	6.1	200	1.6
8	6.1	200	0.2
9	4.7	200	0.4
10	4.9	200	0.1
11	4.7	200	1.5
			Average 0.8

* Total "saturation dose" 800 or 900 mg. l-ascorbic acid over a 4 or 5 day period.
† Four males and 7 females in each group. Birth weights ranged from 1.66 to 2.38 Kg.
‡ Six to 7 days after "saturation" dose.

in the first week and to increase the dose to 75 or 100 mg. on the first two or three days after cow's milk feedings are instituted.

The space accorded to the artificial feeding of premature infants in this presentation requires an explanation. I shall therefore digress for a moment to discuss the relative merits of human milk and low fat cow's milk mixtures as sources of food for these subjects. On purely physiologic grounds, unmodified human milk cannot be considered the ideal food for premature infants, for the following reasons: 1. It is a relatively dilute feeding, and it may therefore predispose the infant to increased intestinal peristalsis and diarrhea, abdominal distention and

respiratory embarrassment. 2. It is relatively high in fat, and, as has been shown, the gastrointestinal tract of the premature infant tolerates fat poorly. 3. It is low in mineral content, particularly in calcium and phosphorus, and there is abundant evidence to prove that even though all of the calcium and phosphorus contained in the daily amounts of human milk ordinarily ingested by the premature infant were completely absorbed from the alimentary tract and utilized the amounts would still be insufficient to meet the demands for bone growth during the first year as determined by chemical analyses of the bones of fetuses and studies of mineral retention. 4. It is relatively low in protein, and evidence has been presented which shows that augmentation of the protein intake is accompanied by an increased alimentary absorption of the extra protein ingested. The rapid rate of body growth of premature infants implies the desirability of a correspondingly high protein intake for the manufacture of the needed extra protoplasm.

The criticisms leveled at unmodified human milk as the ideal food for premature infants are, however, offset by a number of theoretic and practical advantages: 1. One may reason teleologically that a food supplied by nature in the form of mother's milk is biologically to be preferred to any form of artificial food. The absence of tangible proof of this point is considered by the proponents of human milk to be evidence of a lack of knowledge rather than evidence for its nonexistence. 2. There is suggestive but not conclusive evidence that immune substances may be transmitted in the breast milk and particularly in the colostrum. 3. Nursing at the breast after discharge from the hospital has many practical and economic advantages. The absence of expense, the simplicity and the avoidance of the many procedures required to prepare and sterilize cow's milk in the home weigh heavily in favor of breast feeding. 4. The physiologic and psychologic benefits to the mother of suckling her infant at the breast cannot be gainsaid. Even under the best of circumstances, the unexpected birth of a prematurely born baby is associated with intense emotional stress to the mother. She is rushed to the hospital, often before adequate arrangements have been completed for the care of the infant at home; her baby is removed to a special nursery immediately after birth; she learns that his chances of survival are poorer than if he had been born at term; she observes the other mothers suckling their babies and she is not even permitted to see her infant until she is able to get out of bed, when she is allowed the dubious pleasure of viewing her offspring through a glass window. After a protracted period of similar depressing experiences, the infant is suddenly thrust upon her when she is still disturbed and unprepared to meet the added responsibilities. It is perfectly obvious, without further discussion of the point, that satisfying the biologic urge to suckle her young is a wholesome experience and should be encouraged. 5.

Finally, human milk has a low content of electrolytes, and the renal excretion of these substances may be better handled in this form by the premature infant, whose kidneys have been shown to be less efficient excretory organs than those of full term infants.

I should like to close this digression on the relative merits of human and cow's milk as the ideal food for premature infants by suggesting that in hospital practice or when human milk is not available except at great expense, a cow's milk mixture low in fat is an adequate substitute.

Figure 3 is a group of serial photographs of the infant whose clinical record was depicted in figure 1. The first picture (fig. 3 *A*) was taken on the eighteenth day of life, when the infant weighed 766 Gm. (1 pound 11 ounces). It will be noticed that her length closely approximates that of the adjacent 12 inch ruler.

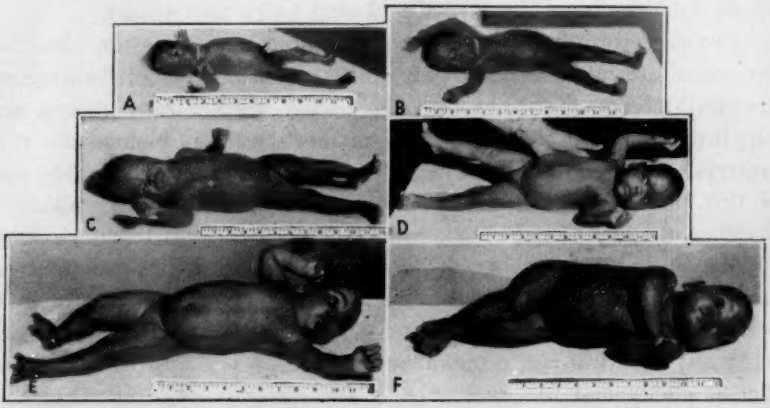

Fig. 3.—Serial photographs of the patient: *A*, at 18 days; *B*, at 51 days; *C*, at 87 days; *D*, at 106 days; *E*, at 5 months; *F*, at 6 months.

The next four pictures (fig. 3 *B*, *C*, *D*, and *E*) were taken on the fifty-first, eighty-seventh and one hundred and sixth days and at 5 months. The respective weights on these days were 1,374, 2,580, 3,140 and 4,580 Gm. The improved appearance and gain in growth are apparent in the successive photographs.

The last photograph (fig. 3 *F*) was taken on October 17, when the infant was exactly 6 months old. Her weight then was 5,100 Gm. (11 pounds 3 ounces) and her height 57 cm. (23 inches). Her bodily proportions were normal for her age, the circumference of the chest exceeding that of the head by 0.5 cm. Roentgenograms of the long bones showed no evidence of rickets. At 6 months she was able to hold her head up without support and to sit up with support, in general was alert and cheerful and showed no signs of mental retardation.

The brief description of the course and management of this infant is presented as a means of illustrating in concrete form the essential elements which constitute good postnatal care for all premature infants.

Preparations for the birth of the infant include provisions for adequately heating the delivery room, receiving blankets and bed to avoid chilling; preparedness for resuscitation, comprising apparatus for suction of foreign material from the respiratory passages (a soft catheter or a Flagg apparatus), stimulants and oxygen, and the attendance of skilled medical and nursing personnel. Facilities should be available for transporting the infant from the delivery room to the premature unit in the form of a heated bed on wheels, preferably equipped with a device for administering oxygen.

There should also be adequate accommodations for premature infants, which include separate unit space for the use of these babies, constant medical supervision, a sufficient number of properly qualified nurses, appropriate facilities for providing proper space, air, light, temperature, humidity and ventilation and, above all, provisions for isolation. Individualized care with approved methods of aseptic technic can be carried out effectively only if sufficient supplies are at hand to permit separate care for each infant. The problems of feeding have already been amply considered.

I should like now to discuss briefly the last item in table 2, to which reference has already been made. When this infant was discharged from the hospital, all measures for instruction of the mother in the care of the infant and an appraisal of the home had been completed. These details were cared for by the public health nurses and social workers. The first contact with the mother was made in the hospital a few days after the birth of the baby. Three days prior to the discharge of the infant from the hospital, a social worker visited the home and appraised its suitability to receive the infant. During this visit the mother was instructed in regard to necessary equipment, including a suitable bed for the infant, adequate heat for its room, proper refrigeration of the food and utensils for preparing it. The technic of actual feeding of the infant had been demonstrated to the mother in several visits to the hospital prior to discharge of her child. During these visits she was permitted to handle and feed the infant. After the discharge of a premature infant, continuous medical supervision is insured by a special premature follow-up clinic, and close contacts are maintained with the home through social workers and public health nurses. I have described this aspect of the postnatal care of a premature child in some detail because it is the one most likely to be neglected, although so far as morbidity is concerned it ranks in importance with other and better attended features.

That the satisfactory outcome obtained in this infant with proper postnatal care is not unique is demonstrated by a careful analysis of

the records of mortality and morbidity of all the premature infants born at the New York Hospital. The uncorrected mortality rate of 905 infants who were admitted to the premature unit was 32 per cent; the rate for infants whose birth weights were less than 1,500 Gm. (3.3 pounds) being 70 per cent (152/217) and for those above 1,500 Gm. 20 per cent (141/688). These figures strikingly illustrate the close relationship between birth weight and viability and stress the importance of utilizing all available obstetric measures to prolong the gestational period in utero. Another indication of the relative importance of prenatal and intranatal influences on viability are the figures for deaths occurring during and after the first forty-eight hours of life. These figures for the group of 905 infants were 23 per cent and 9 per cent, respectively. Finally, the results of autopsies of 266 of the 293 infants who died again reveal the prominent role of antenatal and intranatal influences on the mortality of premature infants. By far the most frequent causes, in descending order, were intracranial hemorrhage, congenital anomalies and pulmonary atelectasis.

Comparable studies on the morbidity of the surviving group of premature infants were conducted by Drs. McKee, Koenig, Huse and Benton [1] in our clinic. These studies reveal that the chances of these infants to develop into healthy and fit persons are not appreciably less than those of infants born at term. Besides careful periodic clinical check-ups carried on for the first three years of life, these observers utilized such objective criteria as anthropometric measurements, fluoroscopic examinations, electrocardiograms and intelligence tests, including Gesell developmental schedules, the Merrill-Palmer preschool scale and the revised Stanford-Binet scale. Their conclusions that with good postnatal care premature infants in general present no greater difficulties than full term infants are in accord with the best published evidence, as summarized by Gesell, that prematurity of birth in itself does not significantly distort, hasten or retard the course of mental and physical development when the age of the infant is reckoned from conception.

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1. McKee, T.; Koenig, H.; Huse, B., and Benton, A. L.: Morbidity and Development, personal communication to the author.

SERUM SICKNESS AND ANAPHYLAXIS

ANALYSIS OF CASES OF 6,211 PATIENTS TREATED WITH HORSE SERUM FOR VARIOUS INFECTIONS

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NEW YORK

(Concluded from p. 143)

MISCELLANEOUS COMPLICATIONS

About 2 per cent of the patients had chills, which were never severe and were followed by a rise in temperature of 2 to 4 degrees (F.) above normal. Usually the chills appeared just prior to the rash or soon after. Fischer [179] observed a child born dead to a normal mother ill with serum sickness. Necropsy showed petechial hemorrhages. In a similar case of his, the child survived sixteen hours and autopsy revealed profuse hemorrhages in the brain, the kidneys and the adrenal capsules. Brown [180] reported the only blood dyscrasia; it developed immediately after an attack of accelerated serum sickness in a previously healthy 14 year old boy who received a prophylactic inoculation of tetanus serum. He had received a similar injection of tetanus serum two years before. He died in four weeks, with generalized adenopathy, splenomegaly and a white blood cell count of 400,000, mostly lymphocytes. Of course, the factor of possible coincidence must be considered in this signal case. A remarkable case was reported by Pagniez and Lerond also.[181] In their case the onset of jacksonian seizures associated with serum sickness revealed a secondary latent tumor of the brain.

SECONDARY INJECTIONS

After a secondary injection the inoculated area often began to swell within a few minutes to an hour, and became itchy and slightly tender, with an occasional burning sensation. The reaction lasted a few days to two weeks. Such swelling occurred much more frequently when the secondary inoculation was administered into the same site as the primary

179. Fischer, E.: Fruchttod bei Serumkrankheit der Mutter, Zentralbl. f. Gynäk. **48**:2203 (Oct. 4) 1924.

180. Brown, E. J.: Acute Lymphatic Leukemia After Tetanus Serum, J. A. M. A. **62**:1473 (May 9) 1914.

181. Pagniez, P., and Lerond: Crises d'épilepsie bravais-jacksonnienne apparues à l'occasion d'accidents sériques chez un malade porteur de tumeur cérébrale secondaire latente, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:55 (May 5) 1927.

injection and usually when it was done a week after the first, though occasionally after some other interval. In 1 case edema spread to the abdomen, the scrotum and the penis, followed on the seventh day by gangrene, the so-called Arthus phenomenon.[32] In another case the buttock became swollen to three times normal size.

The patient was a nurse who had received diphtheria antitoxin outside the hospital the day before. On the day of her admission, unwittingly, I gave the second dose of antitoxin into the same buttock. In an hour she began to complain of pain and slight itching in the same region. On examination the inoculated area was slightly swollen, tender and pinkish. Eighteen hours later the buttock was immense, with the swelling extending up to the lower dorsal vertebrae and the abdomen and as low as the knee on the corresponding side. The skin was red, tense and shiny. There was also a rise of 3 degrees (F.) in temperature. The swelling began to abate after thirty-six hours, but some of it persisted for two weeks. Fever disappeared in two days.

Passive Sensitization to Horse Serum Transferred Through the Use of Human Convalescent Serum.—A remarkable instance of sensitization to horse serum was experienced in the following case:

S. Z., a boy of 2 years, was admitted to the hospital with a mild attack of scarlet fever on the fourth day of illness. He had never been sick before, nor had he ever had toxin-antitoxin inoculations. The rash was fading; so a Schultz-Charlton test was not performed. The reaction to the Dick test was negative, but that to the Schick test was positive. The boy had an uneventful course until the nineteenth day, when measles broke out in the ward and he was given 6 cc. of convalescent measles serum into the left buttock. To this he showed no reaction.

On the twenty-ninth day, in the evening, the patient had a temperature of 102 F. and follicular tonsillitis.

On the thirtieth day, the tonsillitis was worse, and in view of the positive reaction to the Schick test diphtheria antitoxin (10,000 units) was administered into the left buttock after negative reactions had been given to intradermal and conjunctival tests with horse serum (dilution 1:100). Three hours later the temperature rose to 106.4 F. and there was slight swelling of the left buttock.

On the second day after the injection, the buttock was slightly more swollen and tender. The patient was acutely ill. (A culture from the throat showed hemolytic streptococci predominating.)

On the third day, anuria began. This lasted twenty-four hours. A transfusion of 130 cc. of blood was given, with no reaction.

On the fourth day, the swelling of the buttock was increasing.

On the fifth day, the swelling of the buttock was extending to the thigh, the scrotum and the penis.

On the sixth day, swelling of the penis was greater; that of the thigh was less. There was edema spreading over the abdomen, which was distended.

On the seventh day, the swelling of the penis was subsiding. The buttock was getting discolored.

On the tenth day, the patient was more alert, but edema of the abdomen persisted. The skin over the thigh was beginning to break down.

On the eleventh day, there was beginning necrosis of the buttock. The temperature was normal for the first time; it had been fluctuating from 104 to 98.8 F.

From the twelfth to the fourteenth day, the gradually increasing necrosis necessitated surgical intervention.

On the forty-second day, the wound had finally healed, resulting in a large deep scar.

For a while this case proved puzzling, for development of the Arthus phenomenon following the first injection of serum not only had never been reported but seemed impossible. However, having obtained the measles serum myself from patients with scarlet fever who had previously had measles, I discovered that 1 of the 3 who had contributed to this pool of serum had been treated three weeks previously with scarlet fever serum. This makes the first case on record in which the Arthus phenomenon followed passive transfer in a human being, although Nicolle [182] produced it in rabbits in 1907. With the advent of convalescent and pregnant mares' serums together with other glandular extracts coming into general use, sensitization will undoubtedly be more common. However, Goodall and associates [183] stated that if the blood or the serum is forty-eight hours old there is no danger of passive sensitization. This was refuted in this case, because the serum was four days old, while Lichtenstein [184] found hay fever reagin present in dry serum after fourteen months. It may be of interest to add that Voss,[185] after taking serum from patients recently recovered from serum sickness, observed that when he injected it during the first three days after a dose of horse serum a small wheal arose but that if the injection was made after the fourth day the small wheal in some cases spread to a generalized rash and that if the injection was made after the eighth day a generalized immediate reaction sometimes followed. Serum sickness was seen also by Marie [186] after administration of antityphoid convalescent serum and by Tezner and Reiter [187] as well as by me after injection of convalescent measles serum obtained from patients who had not received horse serum, while Fox reported it in 1 per cent of 424 patients who received pooled convalescent scarlet fever serum.

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182. Nicolle, M.: Contribution à l'étude du "phénomène d'Arthus," Ann. Inst. Pasteur **21**:128 (Feb.) 1907.

183. Goodall, J. R.; Anderson, F. O.; Altimas, G. T., and MacPhail, F. L.: An Inexhaustible Source of Blood for Transfusion and Its Preservation, Surg., Gynec. & Obst. **66**:176 (Feb.) 1938.

184. Lichtenstein, M. R.: The Preservation of Reagin in Dried Serum, J. Allergy **4**:239 (May) 1933.

185. Voss, E. A.: Das Prinzip der inversen Anaphylaxie als Methode des Antikörpernachweises beim Menschen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **94**:281 (Nov.) 1938.

186. Marie, P. L.: Accidents sériques chez l'homme consécutifs à l'injection intraveineuse de sérum humain, Compt. rend. Soc. de biol. **79**:149 (Feb. 5) 1916.

187. Tezner, O., and Reiter, F.: Ueberempfindlichkeitserscheinungen nach Injektion arteigenen Serums, Ztschr. f. d. ges. exper. Med. **72**:666 (Aug. 7) 1930.

Arthus Phenomena Reported in the Literature.—In Borovsky's [188] case the gangrene was in rather an unusual location, because in all previous cases reported it developed at the site of the last injection. This was the persistent finding of Arthus, although he occasionally saw gangrene following a subcutaneous injection when the first injection or injections had been made into the peritoneum. Nevertheless, gangrene occurred much more frequently if the injections were given into the same site. Seegal, Seegal and Jost [189] produced it in the pericardium, heart and aorta of the rabbit; Busson [190] and Opie,[191] in the lungs; Long and Seyfarth,[192] in the testicle; Hepler and Symonds,[193] in the kidney; Arslan,[194] in the oropharyngeal mucosa; Shapiro and Ivy,[195] in the stomach; Alessio [196] and Choi,[197] in the liver; Longcope,[198] Rössle [199] and Klinge,[200] in the peritoneum; Davidoff and associates,[201] in the brain;

188. Borovsky, M. P.: Arthus Phenomenon, Am. J. Dis. Child. **40**:1364 (Dec.) 1930.

189. Seegal, D.; Seegal, B. C., and Jost, E. L.: The Arthus Phenomenon, J. Exper. Med. **55**:155 (Jan.) 1932.

190. Busson, B.: Ueber Eiweissanaphylaxie von den Luftwegen aus Wien, Klin. Wchnschr. **24**:1492 (Oct. 26) 1911.

191. Opie, E. L.: Inflammatory Reaction of Immune Animal to Antigen (Arthus Phenomenon) and Its Relation to Antibodies, J. Immunol. **9**:231 (July) 1924; Desensitization to Local Action of Antigen, ibid. **9**:247 (July) 1924; Acute Inflammation from Antibody in Animals Previously Treated with Antigen, ibid. **9**:255 (July) 1924; Pathogenesis of Specific Inflammatory Reaction of Immunized Animals: Relation of Local "Sensitization" to Immunity, ibid. **9**:259 (July) 1924.

192. Long, E. R., and Seyfarth, M.: The Testicle as an Indicator of Allergy in the Hypersensitiveness of Infection and Anaphylaxis, Am. Rev. Tuberc. **9**:254 (May) 1924.

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194. Arslan, K.: Il fenomeno d'arthus nella mucosa orofaringea, Arch. ital. di otol. **48**:18 (Jan.) 1936.

195. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer: Experimental Production of Gastric Ulcer by Local Anaphylaxis, Arch. Int. Med. **38**:237 (Aug.) 1926.

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198. Longcope, W. T.: The Production of Experimental Nephritis by Repeated Protein Intoxication, J. Exper. Med. **18**:678 (Dec.) 1913; Insusceptibility to Sensitization and Anaphylactic Shock, ibid. **36**:627 (Dec.) 1922.

199. Rössle, R.: Ueber die Merkmale der Entzündung an allergischen Organismus, Verhandl. d. deutsch. path. Gesellsch. **19**:18 (March) 1923.

200. Klinge, F.: Die Eiweissüberempfindlichkeit (Gewebs-Anaphylaxie) der Gelenke, Beitr. z. path. Anat. u. z. allg. Path. **83**:185 (Nov. 19) 1929.

201. Davidoff, L. M.; Seegal, B. R., and Seegal, D.: The Arthus Phenomenon, J. Exper. Med. **55**:163 (Jan.) 1932.

TABLE 28.—*Cases of the Arthus Phenomenon Reported in the Literature*

Author	Age	Sex	Previous Injection of Serum	Present Serum	Infection of the Upper Part of the Respiratory Trace	Onset of Gangrene	Comment
von Pirquet and Schick [64].....	Child	F	Diphtheria: 10 cc., 3 yr.; 1 cc., 10 days; 8 cc., 4 days	Diphtheria: 8 cc.	Yes	Third day	Only skin necrosis on abdomen
Lucas, W. P., and Gay, F. P.: J. M. Research **15**: 251, 1909	Children	..	Diphtheria prophylaxis: 3 weeks; another 4 separate injections at intervals of 3 weeks	Diphtheria	No	Not stated	Subcutaneous injection of diphtheria antitoxin given prophylactically to 49 children every 3 weeks; slight skin necrosis developed in 2; not stated if same site was used
Hegler, C.: Klin. Wchnschr. **2**: 698, 1923	23	F	Diphtheria: 8 days left leg	Diphtheria: right buttock	Yes	Tenth day	Only skin necrosis
Gatewood and Baldridge [204].....	24	F	Toxin-antitoxin: 9 mo.; diphtheria: 20,000 units, right buttock, 9 days	Diphtheria: 40,000 units, left buttock; small dose, left arm	No	Fifth day	Massive gangrene; serum sickness for 3 days when swelling of uvula and palate developed and cultures were still positive; antitoxin given again; operation done and patient recovered; left arm became red and swollen in 5 days, but there was only local necrosis on eightieth day
Meleney, F. L.: Ann. Surg **91**: 287, 1930	8	F	Scarlet fever prophylaxis: left buttock, 4 days	Scarlet fever: right buttock	Yes	Fifth day	Massive gangrene; operation done; large deep scar
Borovsky [188]	2	M	Diphtheria: 17 days, buttocks	Diphtheria: intravenously and intramuscularly, left arm	Yes	Third day	Only a small area appeared on dorsum of left hand; it sloughed off
Tumpeer, Matheson and Straus [210]	4	Not stated	Toxin-antitoxin 4 yr.: Diphtheria, left buttock, 1,000 units, 4 days	Diphtheria: 30,000 units, right buttock	Yes	Ninth day	Massive gangrene; operation done; patient died; no necropsy
Irish and Reynolds [212].....	28	M	Toxin-antitoxin: 18 mo.; meningococcus: left buttock, 15, 10 and 6 days; right buttock, 16, 14 and 5 days	Meningococcus: both buttocks	Yes	Tenth day, left; eleventh day, right	Massive gangrene; no operation; patient died; no necropsy
Ross [205]	4	M	Tetanus prophylaxis: 4 days (site not stated)	Scarlet fever: right buttock	No	Seventh day	Massive gangrene; scarlatiniform rash, emesis and fever; condition thought to be scarlet fever and serum administered; rash disappeared in a few hours; patient died; no necropsy
Kohn, McCabe and Brem [207].....	12	F	Toxin-antitoxin, 7 yr.; diphtheria: 10,000 units, 4 days; 10,000 units, 2 days, right buttock	Diphtheria: 15,000 units, right buttock	Yes	Fourth day	Massive gangrene; had general urticaria 5 hr. after first dose of serum; operation done; tissue showed acute and subacute inflammation with marked edema and foci of necrosis; blood vessels had areas of thrombosis and necrosis; large deep scar; local and blood cultures negative
Gougerot and Blum [206].....	21	M	Tetanus: 3 yr. (site not stated)	Tetanus: low in the back	No	48 hours	Immediate reaction; pseudophlegmon in 24 hr.; phlegmon in 48 hr., several centimeters in diameter; phlegmon sloughed off on sixtieth day and healed on seventy-second day
Toomey and Kimball [208].....	Not stated	Not stated	Not stated	Scarlet fever	Not stated	Not stated	No details given

Landouzy and associates [202] and Schlechter and Schwenker,[203] in the joints. However, in all these experiments the reaction appeared at the site of the last injection. In 2 cases, namely that of Gatewood and Baldridge [204] and that of Ross,[205] serum sickness beclouded the diagnosis, and led to subsequent administration of an unnecessary dose of serum, which caused massive gangrene and 1 death. Cases of Ross and of Gougerot and Blum [206] disproved Kohn, McCabe and Brem's [207] contention that massive gangrene occurs only in patients who have simultaneous acute infection of the upper respiratory tract. If a common denominator is sought, fever can be chosen, on account of its presence in every case. Auer [208] observed that if he rubbed a rabbit's ear with xylene and then reinoculated the animal with horse serum intraperitoneally or into the erector spinae muscles gangrene often developed in the irritated ear. He explained this with the statement that the inflamed ear was reinoculating itself with antigen from the blood stream. Later Menkin [209] confirmed Auer's work, when he demonstrated that antigen accumulated in inflamed areas. These observations would help to solve the problem presented by Borovsky's case if some infection had been present on the dorsum of the left hand. He had, however, made no comment on the condition of the particular hand prior to the injection.

The *raison d'être* of the Arthus phenomenon is thought to be the interaction of the antigen and the antibody in that particular region, for its development in rabbits according to Opie and in monkeys according to Kopeloff and Kopeloff corresponds to the presence of precipitin in high titer. This may explain the difficulty encountered in attempting to produce it in animals in which precipitin develops in low dilution, such as

202. Landouzy, L.; Gougerot, H., and Salin, H.: Arthrites séreuses bacillaires expérimentales, Rev. de méd. **30**:857 (Nov.) 1910.

203. Schlechter, H., and Schwenker, G.: Ueber die Beziehungen der Eosinophilie zur Anaphylaxie, Deutsches Arch. f. klin. Med. **108**:405 (Nov.) 1912.

204. Gatewood, W. E., and Baldridge, C. W.: Tissue Hypersensitiveness Following Administration of Toxin-Antitoxin: Phenomenon of Arthus, J. A. M. A. **88**:1068 (April 12) 1927.

205. Ross, F. E.: The Arthus Phenomenon: Report of a Case, J. A. M. A. **103**:563 (Aug. 19) 1934.

206. Gougerot, H., and Blum, P.: Phénomène d'Arthus nécrotique après une réinjection de sérum antitétanique, Arch. dermat. et syph. d. l'Hop. St. Louis **10**:67 (March) 1938.

207. Kohn, J. L.; McCabe, E. J., and Brem, J.: Anaphylactic Gangrene Following Administration of Horse Serum: Arthus or Shwartzman Phenomenon? Am. J. Dis. Child. **55**:1018 (May) 1938.

208. Auer, J.: Local Autoinoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, J. Exper. Med. **32**:427 (Oct.) 1920.

209. Menkin, V.: Studies on Inflammation, J. Exper. Med. **52**:201 (Aug.) 1930.

the guinea pig, the rat and the dog. This possibly may also be the reason why the phenomenon in certain human beings is prone to develop, since the individual antibody response is known to have marked variations. However, thus far, except for the one determination of Tumpeer and Cope,[210b] demonstrating the presence of the precipitin in a dilution of 1 : 32, no one has made a study of the precipitin titer in these patients. The patient of Tumpeer and Cope went into shock one hour after a transfusion and died two hours later. For this reason, they suggested that the Arthus phenomenon may be a transfusion hazard, because both the donor and the recipient were of the same blood grouping (Jansky 1) with agglutinin and hemolysin compatibility. Their serums, however, were not crossed. The authors stated that the donor's serum showed no reaction with diphtheria antitoxin but did not state when the serum of the donor was obtained for the test. If perchance it was taken days after the transfusion, the result would be nullified, for if the donor had eaten horse meat a day or two before the transfusion the shock could easily have been due to anaphylaxis, but with such a lapse of time, as observed by Bernard, Debré and Porak,[211] precipitins might have disappeared from the circulation. Further, patients observed by Kohn, McCabe and Brem, by Irish and Reynolds [212] and by me had transfusions without any reactions whatsoever. The possibility may be that the patient of Bernard and associates, like that of Carrington and Lee,[213] who also died after a transfusion, may have been sensitive to an uncommon allergen. Witness the case of Altimas and McPhail,[183] in which urticaria developed while the patient was receiving a transfusion from a donor who had had a drink of gin just before. The patient said the only thing that ever gave her hives was gin, which she had not had for fifteen years. On the other hand, Stewart and Bates [214] saw severe shock asso-

210. (*a*) Tumpeer, I. H.; Matheson, A., and Straus, D. C.: Arthus Phenomenon in a Syphilitic Child, J. A. M. A. **96**:1373 (April 25) 1931. (*b*) Tumpeer, I. H., and Cope, E. J.: The Arthus Phenomenon: A Serologic Study in a Syphilitic Child with a Fatal Reaction to Transfusion, Am. J. Dis. Child. **45**:343 (Feb.) 1933.

211. Bernard, L.; Debré, R., and Porak, R.: Sur la présence d'albumine hétérogène dans le sang circulant après l'ingestion de viande crue, Compt. rend. Soc. de biol. **73**:66, 1912; Sur la présence de l'albumine hétérogène dans le sang circulant après l'injection intrarectale de sérum équin, ibid. **73**:207, 1912.

212. Irish, H. E., and Reynolds, S. C.: Massive Anaphylactic Gangrene: Arthus Phenomenon, J. A. M. A. **100**:494 (Feb. 18) 1933.

213. Carrington, G. L., and Lee, W. E.: Fatal Anaphylaxis Following Blood Transfusion, Ann. Surg. **78**:1 (July) 1923.

214. Stewart, W., and Bates, T.: Urticaria During Blood Transfusion, Lancet **1**:319 (Feb. 5) 1938.

ciated with urticaria in a woman sensitive to shellfish following a transfusion from a donor who had eaten shellfish the previous night. The question of Forssman's [215] antigen and antibody likewise remains a consideration, as well as some other unknown antigen-antibody union, since only recently Landsteiner and Wiener [216] discovered Macacus rhesus antigen (Rh) in many samples of human blood.

In 5 of 8 cases in which the site of the injection was reported, the second injection was not given into the same site as the first. However, in both the cases which occurred at the Willard Parker Hospital, viz. that of Kohn and associates and my own, the injections were given into the same site. Gatewood and Baldridge's article implied that in their case the Arthus phenomenon was due to inoculations with toxin-antitoxin which were given nine months previously. This inferential conclusion is extremely doubtful, because their patient had received diphtheria antitoxin nine days before the last injection, which closely corresponded to the interval found in every case of the Arthus phenomenon ever reported.' The only case in the literature in which the patient was supposed to have had the Arthus phenomenon after the first injection of horse serum following toxin-antitoxin inoculations was that of Maroney. However, his patient, a woman, had no local symptoms until the eighth day after the administration of diphtheria antitoxin, when serum sickness appeared, and although there was some discoloration at the site for a few days, no necrosis followed. Of course, if taken in a broad sense, the reaction to every second injection of serum, according to Zinsser, can be called an Arthus phenomenon. However, the term Arthus phenomenon, I believe, ought to be reserved, particularly with regard to human beings, to designate only the end result, which is gangrene, in contradistinction to the various preceding stages leading up to this phenomenon. Furthermore, if the mechanism is overlooked, the possibility exists that it may occur after a first injection if an arterial embolism arises, as reported by Touton,[217] Freudenthal [218] and Gammel [219] after

215. Forssman, J.: Die Herstellung hochwertiger specifischer Schafhämolysine ohne Verwendung von Schafblut, Biochem. Ztschr. **37**:78, 1911.

216. Landsteiner, K., and Wiener, A. S.: Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223 (Jan.) 1940.

217. Touton, K.: Zoster femoralis im Anschluss an eine intramusculare Salicylquecksilberinjektion, Arch. f. Dermat. u. Syph. **21**:775, 1889.

218. Freudenthal, W.: Lokales embolisches Bismogenol-Exanthem, Arch. f. Dermat. u. Syph. **147**:155 (April) 1924.

219. Gammel, J. R.: Arterial Embolism: An Unusual Complication Following the Intramuscular Administration of Bismuth, J. A. M. A. **88**:998 (March 26) 1927.

inoculations with mercury and bismuth. Moreover, Cohen and Waterstone [220] recently observed local necrosis following the repeated injections of adrenal extracts into the same site but could not produce it with a synthetic preparation. However, according to the brilliant investigations of Landsteiner [221] on the development of haptenes, following the work of Obermayer and Pick,[222] the possibility exists that this may follow even inoculation with a synthetic preparation, as it is nigh impossible to predict what combination may arise with the tissues or the blood in some persons after repeated injections of a given substance. Local necrosis was observed by Zinsser and Grinnell [223] even following repeated injections of bacterial extracts. The exact mechanism of the Arthus phenomenon was best described by Schenck and Abel.[224] These investigators studied the living blood vessels and capillaries in the rabbit ear and noticed that when the specific allergen, horse serum, made contact in the given area there was a slowing of the blood stream leukocytes, which accumulated in the capillaries and adhered to the wall and occasionally formed large clumps and minute emboli. If the local contact was prolonged, thrombosis and necrosis followed.

DIAGNOSTIC INTRADERMAL TEST

The last but most important factor in serum sickness and anaphylaxis next to repeated injections is the person as determined by the intracutaneous sensitivity test with horse serum. This was first used by Moss,[225] in 1910, although Blackley [226] had started to use the scratch method in his pollen studies in 1873. In the group given diphtheria antitoxin, when the reaction to the sensitivity test was positive the incidence of serum sickness was four times, the incidence of anaphylaxis three hundred and four and the mortality one hundred and eight times greater than

220. Cohen, A. E., and Waterstone, M. I.: Epinephrine Hypersensitivity: Two Cases, J. Allergy **11**:393 (May) 1940.

221. Landsteiner, K.: Specificity of Serological Reactions, Springfield, Ill., Charles C. Thomas, Publisher, 1936.

222. Obermayer, F., and Pick, E. P.: Ueber die chemischen Gundlagen der Arteigenschaften der Eiweisskörper, Wien. klin. Wchnschr. **19**:327 (March 22) 1906.

223. Zinsser, H., and Grinnell, B.: Further Studies on Bacterial Allergy, J. Bact. **14**:301 (Nov.) 1927.

224. Schenck, H. P., and Abel, R. G.: Anaphylaxis Reaction: Tissue Changes as Observed in Living Tissues in Rabbit, Tr. Am. Laryng. A. **60**:210, 1938.

225. Moss, W. L.: A Cutaneous Anaphylactic Reaction as a Contra-Indication to the Administration of Antitoxin, J. A. M. A. **55**:776 (Aug. 27) 1910.

226. Blackley, C. H.: Experimental Researches on the Causes and Nature of Catarrhus Aestivus (Hay-Fever or Hay-Asthma), London, Baillière, Tindall & Cox, 1873.

when there was a negative reaction to the test. Comparison of the incidence of thermal reaction was precluded by its absence in the group reacting negatively to the sensitivity test. In the group given scarlet fever serum, the incidence of serum sickness was 63 per cent higher in

TABLE 29.—*Positive Reactions to Intradermal Sensitivity Test*

Serum	Cases	Serum Sickness: Rash * No.	Rash * %	Without a Rash No.	Without a Rash %	Thermal Reaction No.	Thermal Reaction %	Anaphylaxis No.	Anaphylaxis %	Death No.	Death %
Diphtheria	142	61	43.0	5	3.5						
	180	..	....	..	...	3	1.6	13	7	1	0.54
Scarlet fever	37	28	75.4								
	39	..	....	..	...	2	5.1	7	18	1	2.60
Meningococcus	3	3	....	..	...	..	...	1			
Tetanus	2	1	....	..	...	..	...	1			
Total	184	93	50.0	5	2.7						
	224	..	....	..	...	5	2.2	22	10	2	0.90
Included test above positively reacting eye	7	4		..		..		3			
Sensitivity test not done or not reported	628	79		3		2		1		1	

* Only cases in which the period of hospitalization was ten days or more were considered.

TABLE 30.—*Negative Reactions to Intradermal Sensitivity Test*

Serum	Cases	Serum Sickness: Rash * No.	Rash * %	Without a Rash No.	Without a Rash %	Thermal Reaction No.	Thermal Reaction %	Anaphylaxis No.	Anaphylaxis %	Death No.	Death %
Diphtheria	2,717	310	11.4	15	0.5						
	3,788	...	....	..	...	..	...	9	0.23	2	0.050
Scarlet fever	1,240	594	46.5	32	2.6						
	1,294	...	....	..	...	81	6.3	7	0.54		
Poliomyelitis	43	29									
	51	..	....	..	...	8	...	1			
Meningococcus	71	54									
	84										
Tetanus	2	2									
	5										
Diphtheria and scarlet fever	114	39	34.0	3	2.6						
	138	...	....	..	...	2	1.4				
Scarlet fever and meningococcus	1	1									
	5										
Total	4,188	1,029	24.5	50	1.1						
	5,365	...	....	..	...	91	1.6	17	0.30	2	0.037

* Only cases in which the period of hospitalization was ten days or more were considered.

persons who gave positive reactions to the test than in those who had negative reactions. The incidence of thermal reaction was about the same, but the anaphylaxis rate was three hundred and thirty-three times greater among the former patients. Comparison of mortality rates was precluded by the absence of death in the patients who had negative reactions.

This increase in the incidence of serum sickness and of anaphylaxis in the patients reacting positively to the sensitivity test was evident in every one of the five years. For example, one year the incidence of serum sickness following inoculations with scarlet fever serum was only 30 per cent but the incidence in the patients who had given positive reactions to the test was 75 per cent, and the incidence of serum sickness following inoculations with diphtheria antitoxin one year was six times greater in the patients who had reacted positively than in those who had not. The conjunctival test was done in 5,005 cases, but only 7 patients gave a positive reaction. In some, besides reddening, edema of the lid occurred, which on occasion closed the eye. Undiluted serum was used for the conjunctival test, but on account of the itching and burning it produced, causing not only children but adults to rub their eyes, it was soon discontinued for a 1 : 10 dilution. For the intradermal test a 1 : 100 dilution was used in all but about 200 cases. This dilution was decided on after serum sickness was seen to break out after a test with undiluted serum followed by sensitization and death in the case reported by Bullowa and Jacobi. However, intradermal tests with undiluted material had previously been known to be followed by death, as in Cooke's [227] case, after administration of 0.1 cc. of glue; in Lamson's case, after injection of 0.1 cc. of ovomucoid (the glue and the ovomucoid each contained only 1 mg. of nitrogen per cubic centimeter) and in Baagøe's [228] case, after a test with egg white. Since 1935, as already noted, 2 deaths have each been preceded by an intradermal test with 0.05 and 0.1 cc. of undiluted horse serum. Up to the present time, 1 : 100 dilution of horse serum has not been associated with a death or an anaphylactic shock except in 1 of the cases in this report,[228a] in which the patient had a mild anaphylactic reaction twenty-five minutes after the test

227. Cooke, R. A.: Studies in Specific Hypersensitiveness: The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injections of Allergens, J. Immunol. **7**:119 (March) 1922.

228. Baagøe, K. H.: Case of Allergic Death Due to Intracutaneous Injection of 0.1 cc. of White of Hen's Egg, Ugesk. f. læger **90**:550 (June 14) 1928.

228a. Another case of anaphylactic shock associated with 1 : 100 dilution of serum was encountered by me in December 1941. This was the most severe anaphylactic shock in my experience. It followed intravenous administration of 1 cc. of 1 : 100 dilution of type XXI antipneumococcus rabbit serum to a 10 year old boy on the seventeenth day after primary injection. In about two or three minutes the patient became comatose and had almost persistent tonic and clonic convulsions for three hours. At the end of this time the convulsions decreased in intensity and frequency, although they lasted for three more hours. In twenty-two hours right hemiplegia developed. This is the smallest amount of serum (0.01 cc.) on record ever to have caused such a severe and nigh fatal reaction. The intradermal and conjunctival tests with rabbit serum 1 : 100 gave negative results on both occasions.

injection. When the reaction to the conjunctival test was positive, the incidence of serum sickness in the group with diphtheria was five times as great as when the reaction was negative, and the anaphylaxis rate was eighteen hundred and sixty times as great. In the group given scarlet fever serum, there were only 2 patients with a positive reaction to the conjunctival test, 1 of whom had a generalized rash twenty-five minutes after an intracutaneous sensitivity test with a 1:100 dilution of horse serum and a marked anaphylactic shock the next day after receiving 0.25 cc. of scarlet fever serum subcutaneously, after a markedly positive reaction to an intradermal test: the reaction to the conjunctival test, however, was not nearly as pronounced as the day before. No more antitoxin was administered; this was rather unfortunate, as sepsis developed and the patient died despite repeated transfusions. This patient happened to be in the ward of a recently appointed physician who was himself greatly alarmed by this severe anaphylactic reaction and who was not aware at the time that a patient became refractory to further injections of the same antigen immediately after recovery from an anaphylactic shock. Serum, however, was rarely given in this refractory or antianaphylactic stage, because with proper hyposensitization anaphylaxis was seen to develop in only 1 case in this entire series. When anaphylaxis did occur, the therapeutic amount of serum had already been administered. However, on occasion it occurred when two different serums were administered in full therapeutic amount. For example, 1 patient had 15,000 units of diphtheria antitoxin administered after she had given negative reactions to intracutaneous and conjunctival tests with horse serum. Immediately after the administration of the antitoxin she complained of abdominal pain, became nauseated and anxious, had release of the sphincters and broke out with a generalized urticaria. Epinephrine gave prompt relief, and fifteen minutes later she received 10,000 units of scarlet fever serum intravenously without any reaction. She did not suffer from delayed serum sickness.

Classification of Persons Giving Positive Reactions to the Intradermal Test.—In the entire series there were 224 patients with positive reactions to the intracutaneous test varying from 1 plus to 4 plus in intensity. One plus indicated only an area of redness less than 1 cm. in diameter; 2 plus, 1 cm. or more in diameter; 3 plus, 2 cm. or more with pseudopodia, and 4 plus, 3 cm. or more with psuedopodia. Of these patients, 47 were hyposensitized, with only 1 failure (no death), in a patient on whom, as previously mentioned, the test was not properly performed. Among the 46 remaining patients, there were only 4 with anaphylaxis, in 1 of whom it was of moderate and in 3 of mild severity. The anaphylaxis of moderate severity appeared forty-five minutes after

the second and remaining dose of serum was given, or one hour and forty-five minutes after the first dose, of 0.25 cc., was given subcutaneously. In 2 of the patients with anaphylactic shock of mild severity, it came about a minute after the second and remaining dose of serum was given, or exactly an hour after the first dose, of 0.25 cc., of antitoxin was administered subcutaneously. In the remaining patient the shock occurred during hyposensitization. There were 12 patients with 3 plus sensitivity, all of whom had received their antitoxin either subcutaneously or intramuscularly in one dose; 1 had anaphylaxis. In the 4 plus class, there were 11 patients. Seven of them received their antitoxin in one dose and 4 had anaphylactic reactions. Four received their serum in divided doses, and 2 had anaphylactic shocks; 1 of these, however, was not properly hyposensitized. The patient in the last group who had anaphylaxis although she was properly hyposensitized received the first two injections subcutaneously, having only a light local reaction after the first and none after the second; however, she broke out with mild generalized urticaria and became anxious and restless almost immediately after the intramuscular injection. Epinephrine gave prompt relief but the patient was given the remaining dose of antitoxin intramuscularly one-half hour later without any reaction. This patient also had given a positive conjunctival test. All of these patients were given the serum subcutaneously or intramuscularly except 1. That patient received it intravenously, intramuscularly and intrathecally daily for six days without once showing a reaction. On the sixth day urticaria broke out, but the administration of serum produced no deleterious effect. This patient was an extremely sick child who had hemolytic streptococcus meningitis as well as streptococcemia associated with scarlet fever; death occurred on the seventh day after the first dose of serum was given.

Route Factor: In considering the route of administration, it was seen that serum sickness was absent in 4 cases after intravenous administration of diphtheria antitoxin but that the incidence of thermal reactions was thirty-three times and that of anaphylaxis ten times greater than after intramuscular administration, although 1 death occurred after intramuscular administration. Of 14 patients who received the serum both intramuscularly and intravenously, serum sickness was present in only 16 per cent, which was only about one third as high an incidence as that found after administration by the intramuscular route; the anaphylaxis rate was only slightly higher. In the groups given scarlet fever serum, there were 35 patients who received the serum intramuscularly; of these, 78 per cent had serum sickness and 14 per cent had anaphylaxis. Only 2 of these patients were given the serum intravenously; 1 had serum sickness and a thermal reaction and 1 had anaphylaxis followed by death.

There was also 1 patient who received the serum both intravenously and intramuscularly; this patient had a thermal reaction and serum sickness. Another patient received the serum intravenously, intramuscularly and intraspinally; this patient also had serum sickness. Recapitulating, there were 18 patients who received diphtheria antitoxin intravenously, with a 12 per cent incidence of serum sickness, a 5 per cent incidence of thermal reaction and a 16 per cent incidence of anaphylaxis. In the group with scarlet fever, there were 4 patients who received serum intra-

TABLE 31.—*Route Factor in Serum Sickness and Anaphylaxis*

Route	Cases	Serum Sickness: Rash No.	Rash %	Without a Rash No.	Without a Rash %	Thermal Reaction No.	Thermal Reaction %	Anaphylaxis No.	Anaphylaxis %	Death No.	Death %
A. Positive Reactions to Intradermal Sensitivity Test											
Diphtheria Antitoxin											
Intramuscular	126	59	46.8	5	3.9						
	162	..	....	..	...	2	1.2	9	5.5	1	0.6
Intravenous	4	..	....	..	...	1	...	2			
Intravenous and intramuscular	12	2	16.0								
	14	..	....	..	...	..	...	1			
Scarlet Fever Serum											
Intramuscular	34	25									
	35	..	....	..	...	..	...	5			
Intravenous	1	1									
	2	..	....	..	...	1	...	1	...	1	
Intravenous and intramuscular	1	1	....	..	...	1					
Intravenous, intraspinal and intramuscular	1	1									
B. Positive Reactions to Conjunctival Test											
Diphtheria Antitoxin											
Subcutaneous	4	3	....	..	...	..	...	1			
Intramuscular	1	1	....	..	...	..	...	1			
Scarlet Fever Serum											
Subcutaneous	2	..	....	..	...	..	...	1			
Intramuscular	1										

venously, with an incidence of serum sickness of 75 per cent, of thermal reaction of 50 per cent and of anaphylaxis and of death of 25 per cent each.

Cases of Spontaneous Sensitivity.—In this group of 224 cases there was only 1 patient with spontaneous sensitivity, namely, to horse serum. This patient was hyposensitized without difficulty. However, there were 2 other patients with a history of allergy; 1 had hay fever and the other had hives, but both gave negative reactions to sensitivity tests. The patient subject to hives had them present on admission, but on the three days after the serum was administered they were much worse. The patient with hay fever did not have serum sickness.

The reason 177 of these patients were not hyposensitized was the fact that patients with severe diphtheria with a positive reaction to an intradermal sensitivity test were reported by Park [229] to have received serum intravenously with 5 having no reaction and 5 only a chill, while anaphylactic shock occurred in a patient who had a negative reaction to a sensitivity test. As a result, he concluded that it was "almost never dangerous" to inject serum if the sensitivity was confined to an areola ½ to 2 inches (1.3 to 5 cm.) in diameter, unless there was evidence of status lymphaticus or a history of allergy. Furthermore, Coca [230] contended that it was useless to apply the cutaneous test or the procedure of hyposensitization when reinjection of serum was indicated. He supported this conclusion by citing the death reported by Tuft following hyposensitization, which, as previously criticized by Mackenzie and Hangar, was not properly performed. These contentions influenced some of the resident physicians to order the serum administered in one dose, no matter what the reaction to the sensitivity test happened to be.

Positive Reactions to Intradermal and Conjunctival Tests Reported in the Literature.—Toomey and August [231] had only about a 2 per cent higher incidence of serum sickness in 121 patients who gave a positive reaction to the intradermal test than in a group of 659 who reacted negatively. However, in a later but smaller series Toomey with Kimball found the incidence to be 20 per cent higher in patients who gave a positive reaction to the test. Davis,[232] after administering diphtheria antitoxin to 200 patients, observed serum sickness in 22 per cent of the 122 who had reacted negatively to the intradermal test and in 28 per cent of 78 who had given a positive reaction. She did not state for how long her patients were followed or whether both groups were followed for the same length of time. Wilson, Wyatt and Bennett,[233] after the administration of scarlet fever serum, saw serum sickness in 92 per cent of 34 patients who had given a positive reaction to the intradermal test and in only 48 per cent of 69 who had given a negative reaction. Spicer,[234]

229. Park, W. H.: Human Hypersensitiveness to Whole Horse Serum or Serum Globulins Following Diphtheria Toxin-Antitoxin Injections: Its Importance, J. Immunol. **9**:17 (Jan.) 1924.

230. Coca, A. F., in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 1012.

231. Toomey, J. A., and August, M. H.: Reactions Following Administration of Diphtheria Antitoxin and Toxin-Antitoxin: Results of Desensitization, J. Prev. Med. **4**:281 (July) 1930.

232. Davis, H. M.: Horse Serum Skin Tests, J. Hyg. **38**:325 (May) 1938.

233. Wilson, J. R.; Wyatt, T. C.; Bennett, J.; Chapman, O. D., and Knolton, C: Serum Sickness: Clinical and Experimental Study; Preliminary Report, New York State J. Med. **34**:915 (Nov. 1) 1934.

234. Spicer, S.: Ophthalmic Test for Horse Serum Sensitivity Contrasted with the Intradermal: Performed on Three Hundred and Fifty-Three Patients, J. Immunol. **15**:335 (July) 1928.

after administration of diphtheria antitoxin, encountered serum sickness in 45 per cent of 54 patients who had given a positive reaction to the intradermal test and in only 12 per cent of 232 patients who had reacted negatively. In this same series, 7 patients reacted positively to the conjunctival test, and every one of these had serum sickness. Sutliff [235] among 291 patients treated with pneumococcus serum found anaphylaxis to be thirteen times more frequent in those who had reacted positively to the intradermal sensitivity test, while Claiborn [236] had 2 patients with anaphylaxis following prophylactic inoculation with tetanus serum among 17 who had given a positive reaction to the conjunctival test. Eleven of these were followed for ten days or more, and 5 had serum sickness. Moreover, among 43 patients with a positive reaction to the intradermal test the incidence of serum sickness was only 21 per cent; this was almost identical with the 20 per cent incidence found in 150 patients with a negative reaction to the test. All of these writers stated that if the reaction to the conjunctival test was positive the reaction to the intradermal test also was positive and was much more reliable in indicating whether an immediate general reaction was to be expected. Peshkin,[237] however, claimed that the conjunctival test often elicited a positive reaction when the reaction to the intradermal test was negative if dry pollen was used.

DIAGNOSIS

Serum sickness is ordinarily simple to diagnose if it is kept in mind. However, when the symptoms are unusual one is apt to consider a disease of the particular region and overlook the protean manifestations with which serum sickness may make its appearance. Repeated blood counts in cases of unexplained fever or adenopathy occurring prior to the rash proved to be of no value, since eosinophilia was observed only in cases in which a rash was present for two or more days. On occasion, even if serum rash is present, it may prove to be a difficult matter to differentiate it from other diseases, and at such times a little patience will be rewarded. Some assistance is offered by Davidsohn's [238] finding

235. Sutliff, W. D.: Constitutional Reaction Immediately After Injection of Concentrated Serum, J. Allergy **1**:156 (Jan.) 1930.

236. Claiborn, L. N.: The Ophthalmic Test for Sensitivity to Horse Serum, J. A. M. A. **98**:1718 (May 14) 1932.

237. Peshkin, M. M.: A Dry Pollen Ophthalmic Test in Pollen Asthma and Hay Fever Patients Negative to Cutaneous Tests, J. Allergy **3**:21 (Nov.) 1931.

238. Davidsohn, I.: Heterophile Antibodies in Serum Sickness, J. Immunol. **16**:259-273 (March) 1929; Further Studies on Heterophilic Antibodies in Serum Sickness, ibid. **18**:31 (Jan.) 1930.

of a high sheep agglutinin titer in the blood of patients with serum sickness and, if confirmed, by Rhodin's [239] observation of a profound drop in the sedimentation rate.

The differential diagnosis between serum sickness and anaphylaxis was based on the time interval. The interval decided on was that of Cooke, who considered a reaction one of anaphylaxis if it occurred within an hour or less after the administration of the allergen. His observation that the shorter the onset the more severe the reaction received substantiation in this study except for the 2 deaths following intramuscular administration. However, a mild local reaction, even if it occurred within the hour, was classified here as one of serum sickness. Of course, a reaction appearing as early as this or even within the next few days would be classified as one of allergy [240] or of accelerated serum sickness. Von Pirquet and Schick were the first to demonstrate that this type of reaction occurred only after secondary injections. When it was seen in cases in which there had never before been any inoculation with serum, other means of sensitization of necessity came into play, e. g. ingestion, inhalation and heredity; these will be treated more fully later.

The differential between a thermal reaction and anaphylaxis at first seems obvious, but at times it is confusing owing to the concurrence of these conditions, although the former is never of any concern until the temperature reaches 107 F. In this series there were 41 patients with anaphylactic shock. Thirty-five of these had associated urticaria; 1, only edema of the face, and 5, no rash or any other apparent allergic sign but collapse and some epigastric pain, emesis or nausea. Of the 5, 4 died, and only 1 had a moderate thermal reaction (106 F.). The question may be raised whether they died from an anaphylactoid reaction,[241]

239. Rhodin, H.: Les courbes des réactions de sédimentation dans la maladie sérique et dans diverses affections épidermiques, Acta med. Scandinav., 1928, supp. 26, p. 36.

240. von Pirquet, C. E.: Allergie, München. med. Wchnschr. **53**:1457, 1906; Allergy, Arch. Int. Med. **7**:259 (Feb.); 383 (March) 1911.

241. Hanzlik, P. J.; Karsner, H. T., and Fetterman, J.: Anaphylactic Phenomena from Thromboplastic Agents, J. Pharmacol. & Exper. Therap. **14**:229 (Nov.) 1919. Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from the Intravenous Administration of Various Colloids, Arsenicals and Other Agents, ibid. **14**:379 (Jan.) 1920; Comparison of Prophylactic Effects of Atropine and Epinephrine in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arsphenamine, ibid. **14**:425 (Jan.) 1920; Effects of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Bronchi of Perfused Lungs, ibid. **14**:449 (Feb.) 1920; Effects of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Surviving Intestine and Uterus, ibid. **14**:463 (Feb.) 1920. Karsner, H. T., and Hanzlik, P. J.: Hemagglutination in Vitro by Agents Which Produce Anaphylactoid Symptoms, ibid. **14**:479 (Feb.) 1920.

but autopsy of 2 of them showed a combination of the guinea pig and the rabbit type of anaphylactic death and, for 1, the canine type as well, with no evident thrombosis. Of the 35 patients with a rash, 9 had also a thermal reaction; 3 had the reaction after intramuscular, 3 after intravenous and 1 after subcutaneous inoculation of scarlet fever serum and 2 after intramuscular inoculation of diphtheria antitoxin. Two of the patients given scarlet fever serum had a positive reaction to a sensitivity test, 1 after intramuscular and 1 after subcutaneous inoculation. Each of the patients with diphtheria had a positive reaction to the sensitivity test.

On the other hand, the symptoms associated with anaphylaxis and with anaphylactoid reaction may be identical except for the rash. This is illustrated in the following case:

P. S., a girl aged 6 years, with no history of allergy and with negative reactions to sensitivity tests, was given 5,000 units of scarlet fever serum intravenously. After 4 cc. was given in about four minutes, she began to feel "sick to her stomach." Administration was stopped for a minute, and she felt better. She was given the remainder of the serum (about 5 cc.) and at the end again complained of a "pain in her stomach." In two minutes she was pale and in shock. The respirations were shallow and the pulse fair and rapid. She was given 1:1,000 epinephrine hydrochloride solution (5 minims [0.3 cc.]), but there was no response. In five minutes she had release of the sphincters, generalized tonic convulsions and glassy eye with pinpoint pupil. She was cyanotic and then purple. The respirations were slow, each taking six to ten seconds. The patient was moribund. The respirations were irregular for three or four minutes. Then the cycle just described was repeated, and in forty minutes she was alert and comfortable. There was no rise or fall in temperature. This was a severe anaphylactoid reaction, but it is common with certain scarlet fever serums.

Anaphylactoid reactions were characterized by the rarity of any thermal reaction, by the absence of a rash, by the frequency and severity of convulsions and by their failure to respond to epinephrine.

Biedl and Kraus [242] were the first to describe a fall of blood pressure, incoagulability of the blood and leukopenia in anaphylactic shock. The coagulation time [242a] may even be twenty-one times longer than normal

242. Biedl, A., and Kraus, R.: Experimentelle Studien über Anaphylaxie, Wien. klin. Wchnschr. **22**:363 (March 18) 1909; **23**:385 (March 17) 1910.

242a. To a certain extent coagulation time can be used as a basis for prognosis. In December 1941, for example, I observed the most severe prolonged anaphylactic reaction in a boy 10 years of age. For two hours he had almost persistent tonic and clonic convulsions; at the end of this time the coagulation time was taken and found to be eight and a half minutes. It was determined again one hour later and found to be only five and a half minutes. About this time the convulsions became much less severe and infrequent, although they persisted for three hours more. The patient recovered.

according to Shattuck.[243] Auer and Robinson [244] demonstrated by means of electrocardiograms that a heart block occurs in rabbits and dogs during anaphylaxis. Whether this was due to spasm of the coronary arteries or to pulmonary obstruction they could not say. A similar reaction was observed by Koenigsfeld and Oppenheimer [245] in guinea pigs. This finding was confirmed by Coca [246] and Drinker and Bronfenbrenner.[247] Airila [248] noticed that the pulmonary pressure increased greatly in rabbits during anaphylactic shock. Vagliano [249] noted that the p_H of the blood serum decreased in anaphylaxis from 7.01 to 6.53 in twenty minutes. A relative observation was made clinically by Hopmann [250] when in a case of acidosis tetany developed during serum sickness. Eggstein [251] observed a reduction of the carbon dioxide capacity of the blood serum in dogs during anaphylactic shock; the capacity often reached as low as 25 volumes per cent. Friedberger [252] and Pfeiffer [253] noted a fall in temperature of as much as 10 degrees (C.) in the guinea pig during anaphylactic shock. However, if a nonfatal dose was given a thermal

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243. Shattuck, H. F.: Studies in Protein Intoxication: I. Blood Coagulation, Arch. Int. Med. **20**:167 (April) 1917.

244. Auer, J., and Robinson, G. C.: An Electrocardiographic Study of the Anaphylactic Rabbit, J. Exper. Med. **18**:450 (Oct.) 1913. Robinson, G. C., and Auer, J.: Disturbances of the Heart-Beat in the Dog Caused by Serum Anaphylaxis, ibid. **18**:556 (Nov.) 1913.

245. Koenigsfeld, H., and Oppenheimer, E.: Elektrokardiographische Untersuchungen beim anaphylaktischen Schock des Meerschweinchens, Klin. Wchnschr. **1**:849 (April 22) 1922.

246. Coca, A. F.: Mechanism of Anaphylaxis Reaction in the Rabbit, J. Immunol. **4**:219 (July) 1919.

247. Drinker, C. K., and Bronfenbrenner, J.: Pulmonary Circulation in Anaphylactic Shock, J. Immunol. **9**:387 (Sept.) 1924.

248. Airila, Y.: Ueber die Ursache der tödlichen Blutdrucksenkung im akuten anaphylaktischen Schock beim Kaninchen, Skandinav. Arch. f. Physiol. **31**:388, 1914.

249. Vagliano, M.: De l'anaphylaxie sérique expérimentale, Thesis, Paris, no. 360, 1924.

250. Hopmann, R.: Serumkrankheit und Tetanie, Klin. Wchnschr. **4**:1810 (Sept. 17) 1925.

251. Eggstein, A.: The Alkali Reserve of the Blood Plasma During Protein Shock, J. Lab. & Clin. Med. **6**:481 (June) 1921; The Alkali Reserve of Blood Plasma During Acute Anaphylactic Shock, ibid. **6**:555 (July) 1921.

252. Friedberger, E.: Die Anaphylaxie mit besonderer Berücksichtigung ihrer Bedeutung für Infektion und Immunität, Deutsche med. Wchnschr. **37**:481 (March 16) 1911.

253. Pfeiffer, H.: Zur Kenntnis der Anaphylaxie und Hämolysinvergiftung, Wien. klin. Wchnschr. **23**:1484 (Oct. 20) 1910.

reaction occurred.[254] One could consider this as a possible prognostic sign, but 2 of the 11 patients with anaphylaxis in whom this occurred died.

MECHANISM

Hamburger and Moro,[255] in 1903, found precipitin in the blood of persons suffering from serum sickness. This was soon confirmed by von Pirquet and Schick, but they also observed that some patients with serum sickness did not have any precipitin in the circulation. C. Wells [256] found a direct correlation between precipitins and serum sickness in patients receiving diphtheria antitoxin. This was confirmed by Longcope,[257] Mackenzie and Leake [258] in cases of serum sickness following the use of antipneumococcus serum. However, H. G. Wells, Fleisher and Jones,[259] Wyard,[260] Tuft and Ramsdell [261] could find no correlation between precipitins and serum sickness. Matsumoto [262] discovered that an animal had no precipitin in the circulation, but still the organs had two to four times as high a precipitin titer as was ever found in the circulation. Why serum sickness develops in certain cases and not in others still remains a mystery. It is possible that in some instances the injected serum forms a combination with probably no relation to the precipitin demonstrable at the present time (a combination is similar to a haptene, as described by Landsteiner), initiating a response manifesting itself in a form known as serum sickness.

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254. Friedberger, E., and Mita, S.: Ueber Anaphylaxie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **10**:216 (July) 1911.

255. Hamburger, F., and Moro, E.: Ueber die biologische nachweisbaren Veränderungen des menschlichen Blutes nach Seruminjektion, Wien. klin Wchnschr. **16**:445 (April 9) 1903.

256. Wells, C. W.: On the Specific Precipitin in the Blood of Persons Injected with Antidiphtheric Horse Serum, J. Infect. Dis. **16**:63 (Jan.) 1915.

257. Longcope, W. T., and Rackemann, F.: Development of Immune Reactions in Serum Disease, Proc. Soc. Exper. Biol. & Med. **13**:101, 1916.

258. Mackenzie, G. M., and Leake, W. H.: Relation of Antibody and Antigen to Serum Disease Susceptibility, J. Exper. Med. **33**:601 (May) 1921.

259. Fleisher, M. S., and Jones, L. R.: Serum Sickness in Rabbits with Manifestations of Serum Sickness, J. Exper. Med. **54**:597 (Oct.) 1931; Precipitinogen and Precipitins in Relation to Appearance of the Reaction, ibid. **55**:79 (Jan.) 1932.

260. Wyard, S.: Precipitins and Etiology of Serum Sickness, J. Path. & Bact. **25**:191 (April) 1922.

261. Tuft, L., and Ramsdell, S. G.: Antibody Studies in Serum Sickness: Study of Sera Secured by Serial Bleeding from Persons Treated with Immune Serum, J. Immunol. **17**:539 (Dec.) 1929; Antibody Response in Human Being After Injection with Normal Horse Serum, J. Exper. Med. **50**:431 (Oct.) 1929.

262. Matsumoto, K.: Ueber das Verhalten des Organpräzipitins bei der Anaphylaxie, Scient. Rep. Gov. Inst. Infect. Dis., Tokyo **6**:145, 1927.

The mechanism of anaphylaxis, on the other hand, is more easily linked up with the antigen-antibody union. However, it is not within the scope of this article to make anything but a cursory résumé of this phenomenon, for since the turn of the century there probably has not been a subject which has had such an enormous amount of work lavished on it as anaphylaxis. For comprehensive reviews the reader is referred to the papers and monographs of Richet, Besredka,[263] Vaughan,[264] Weil,[265] Doerr,[266] Wells and Coca. The antigen-antibody mechanism was first suggested and in part proved by the work of Richet, Gay and Southard [267] and others but was not definitely established until Schultz [268] demonstrated that sensitized smooth muscle reacted to the specific antigen. The relation between anaphylaxis and serum sickness is extremely close, if not identical, for, as this study indicates, the only real difference between the two is the time interval. This identification, however, was objected to by Coca, who preferred to place anaphylaxis in the category of drug reactions. Fortunately, this relation at the present time seems to have been considerably clarified by the researches of Landsteiner; these revealed how different substances, whether carbohydrates, lipids or salts, may become antigens when coupled with some protein.

In the beginning, anaphylaxis was built on the humoral hypothesis, as suggested by Friedemann [269] and Friedberger and Castelli,[270] but was

263. Besredka, A.: Anaphylaxis and Anti-Anaphylaxis, London, William Heinemann, 1919.

264. Vaughan, W. T.: Practice of Allergy, St. Louis, C. V. Mosby Company, 1939.

265. Weil, R.: The Nature of Anaphylaxis and the Relations Between Anaphylaxis and Immunity, J. M. Research **27**:497 (March); **28**:243 (July) 1913; The Mechanism of Anaphylactic Shock, Proc. New York Path. Soc. **14**:238 (Dec.) 1914; The Cellular Interpretation of Anaphylaxis and Immunity, Proc. Soc. Exper. Biol. & Med. **11**:86, 1914; The Analysis of Serum Sickness, Proc. New York Path. Soc. **16**:68 (March) 1916; Studies in Anaphylaxis, J. Immunol. **2**:469 (Aug.); 525 (Oct.) 1917.

266. Doerr, R.: Allergie und Anaphylaxie, in Kolle, W.; Kraus, R., and Uhenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1929, vol. 1, p. 759.

267. Gay, F. P., and Southard, E. E.: Serum Anaphylaxis in the Guinea Pig, J. M. Research **11**:143 (May) 1907; Further Studies in Anaphylaxis, ibid. **14**:17 (July) 1908.

268. Schultz, W. H.: Physiological Studies in Anaphylaxis, J. Pharmacol. & Exper. Therap. **1**:549 (March) 1910.

269. Friedemann, V.: Weitere Untersuchungen über den Mechanismus der Anaphylaxie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**:591 (June 22) 1909.

270. Friedberger, E., and Castelli, G.: Ueber Anaphylaxie: VI. Mitteilung. Weiteres über die Antiserumanaphylaxie, Ztschr. f. Immunitätsforch. u. exper. Therap. **6**:179 (June 22) 1910.

soon given up because of the following facts: Pearce and Eisenbrey [271] demonstrated that anaphylaxis did not occur in dogs given transfusions of sensitized blood but that it did develop in sensitized dogs given transfusions of normal blood. On the other hand, Coca [272] noticed that sensitized guinea pigs were easily shocked, even if all of their blood was removed and followed by a thorough perfusion with solution of sodium chloride. Furthermore, if the blood from a sensitized guinea pig was transfused into a normal guinea pig an incubation interval was necessary before anaphylaxis could be produced. This usually was twenty-four hours, but in some cases it could be decreased to as low as four hours. Similar observations were made by Manwaring on dogs. Then Schultz, in 1911, produced incontrovertible evidence that the mechanism of anaphylaxis was cellular when he demonstrated that the smooth, muscular bowel tissue of a guinea pig contracted on being immersed in its specific antigen. This was further confirmed by Dale [273] on a virgin guinea pig uterus. Vaughan was the first to put forth the idea that the mechanism of anaphylaxis was activated by a protein split product, a so-called zymogen, which developed after the introduction of the serum and which on reintroduction of the serum produced a reaction within the body, after uniting with the newly split protein.

At first the site of this reaction was thought to be in the central nervous system, on account of the convulsions sometimes seen, but this theory was soon discarded when anaphylaxis occurred in decerebrated and pithed animals, in the experiments of Pearce and Eisenbrey. After the experiments of Schultz and Dale the site was finally established as being in the tissues, either in the endothelial or in the myoneural junction or in both. The exact location seems to vary in the different species, depending on the fortuitous distribution of smooth muscle. For example, in the guinea pig it is in the bronchi, in the rabbit in the pulmonary artery and in the dog in the hepatic veins, while in man it may be in any one of these or in a combination of them all.

The manner in which this union of antigen and antibody takes place is believed to be a chemical one by some, but most of the evidence points toward a physical mechanism which has its greatest force in the Schultz-Dale phenomenon. Manwaring [274] claimed the precipitins have no

271. Pearce, R. M., and Eisenbrey, A. B.: The Physiology of Anaphylactic "Shock" in the Dog, J. Infect. Dis. **7**:565 (Aug. 24) 1910.

272. Coca, A. F.: The Site of Reaction in Anaphylactic Shock, Ztschr. f. Immunitätsforch. u. exper. Therap. **20**:622 (March 10) 1914.

273. Dale, H. H.: The Effect of Varying Tonicity on the Anaphylactic and Other Reaction of Plain Muscle, J. Pharmacol. & Exper. Therap. **4**:167 (Jan.) 1913.

274. Manwaring, W. H.; Shumaker, P. W.; Wright, P. W.; Reeves, D. L., and Moy, H. B.: Relation of Anaphylaxis to Immunity, J. Immunol. **13**:63 (Jan.) 1927.

correlation with anaphylaxis, because he demonstrated that if he took blood from a dog found to be immune to anaphylactic shock after repeated injections and transfused this blood into a sensitized dog, the latter became refractory to anaphylaxis after twenty-four hours. However, the precipitin content of the sensitized and that of the immune dog's blood was found to be about the same. This made him conclude that the precipitin and the anaphylactic bodies were not only not the same but unrelated. On the other hand, Culbertson [275] demonstrated that passive sensitization could not be accomplished if the precipitins were removed from the serum. Moreover, even if Manwaring's work should be confirmed by others, it would still not disprove the lack of relationship between these two substances, for in the immune dog the antibody content in the tissues would be saturated, while in the sensitized dog it would not be. One of the findings from the intensive researches of Weil [276] was the fact that the presence of humoral antibodies prevented the union of the antigen with the antibody of the tissues and thus protected the animal from anaphylaxis. However, if these were saturated the colloidal equilibrium in the tissue cells would be changed, allowing some of the antibodies to enter the blood stream with a consequent decrease in the tissues. The result of this action, depending on the amount of antigen introduced and the amount of free antibodies set off into the blood stream as well as the amount of unsaturated antibodies remaining in the tissues, decided whether an anaphylactic response would be elicited. This would also explain why one occasionally observes, as reported by Coca and associates [277] and Rackemann [278] and others, years of freedom from allergic symptoms following hyposensitization in a patient with asthma or hay fever while reagins are still found in the blood and with relatively no change in the intensity of the skin test. Because an exceptional case like this does appear, it does not necessarily vitiate the value of the intradermal test, for no biologic test is perfect.

When hyposensitization is performed, the same sequence of events occurs as has just been mentioned. The antibodies in the blood are gradually saturated, and when they are completely saturated a force is placed on the antibodies in the tissues, causing an exodus of antibodies,

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275. Culbertson, J.: A Quantitative Study of the Precipitin Reaction with Special Reference to Crystalline Egg Albumin and Its Antibody, J. Immunol. **23**:439 (Dec.) 1932.

276. Weil, R.: Desensitization: Its Theoretical and Practical Significance, J. M. Research **29**:233 (Dec.) 1913.

277. Levine, P., and Coca, A. F.: Studies in Hypersensitization: Relation of Skin Sensitivity to Reagin Content of Serum, J. Immunol. **11**:435 (June) 1926.

278. Rackemann, F. M., in discussion on Waldbott, G. L., and Ascher, M. S.: Rapid Hyposensitization, J. Allergy **6**:93 (Nov.) 1934.

which in turn are saturated; if an excess of antigen remains it saturates the remaining antibodies in the tissues. If the latter saturation is done rapidly, the reaction may result in anaphylactic symptoms causing death or a state of antianaphylaxis. If antianaphylaxis supervenes, the antibodies in the tissues are saturated, and the more severe the reaction, the more complete is this saturation, which makes further addition of serum innocuous. This state ordinarily lasts about two weeks but occasionally may last only a day. During anaphylactic shock one of the known products given off is histamine derived from histidine, which is a normal constituent of almost all normal tissues. This was first discovered by Dale,[279] in 1911, who produced anaphylactic-like symptoms by injections of histamine. Sporadically ever since, and especially recently,[280] there has been a fresh interest aroused in trying to blame histamine for the phenomenon of anaphylaxis. This has been thus far unsuccessful, for, although it does produce anaphylactoid symptoms as do agar and many other substances, it is not able to desensitize animals, it contracts the desensitized and relaxes the sensitized virgin guinea pig uterus and it does not increase the coagulation time of the blood.

PREVENTION

This study revealed that the incidence of serum sickness and anaphylaxis was influenced by many factors, namely, the kind of serum, the quantity, the route of administration, the preparation of the serum, the horse producing the serum, repeated injections and the patient. The most important were the kind of serum, repeated injections and the patient, as determined by the sensitivity test. Quantity can be controlled by developing more potent serums. Repeated injections ought to be avoided if the serum can be administered at one time. No interval should elapse between injections, as it is much better to give an additional dose of serum if there is any question as to the negativity of the culture or the lack of improvement in the patient's physical condition. If intramuscular injections are repeated, they should not be given into an area of previous injection. The intradermal and conjunctival tests with horse serum should be done every time the serum is administered unless it is given daily. When serum was given daily, no untoward reaction was ever seen except in 1 patient with diphtheria who suffered a thermal reaction with a rise of temperature to 107.2 F. after intravenous injection of a specific serum. Repeating the sensitivity tests is essential, since

279. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of B-Iminazolylethylamine, J. Physiol. **41**:318 (Dec.) 1911.

280. Karady, S., and Bentsath, A.: Histamingewöhnung und experimentelle Anaphylaxie, Ztschr. f. d. ges. exper. Med. **100**:48, 1936. Farmer, L.: Nonspecific "Desensitization" Through Histamine, J. Immunol. **36**:37 (Jan.) 1939.

the results are known to change. There were 16 patients who on being retested prior to the administration of a secondary injection of serum were found to have a reversal of their reactions to the tests; namely, 12 gave positive and 4 negative reactions. In the former group the change was discovered anywhere from the seventh to the seventy-third day; in the latter, from the second to the eighth day. One patient who had a 3 plus reaction to the sensitivity test showed absence of sensitivity the following day when a small prophylactic dose of serum was administered without a reaction except for a fever response the next three days. Other investigators have noted similar changes. Cowie [281] observed a patient whose reaction became positive after one intradermal test, and Hooker,[282] performing three sensitivity tests on himself in seven years, noticed that the reaction to the last one was positive although he reacted negatively to the first two. One should make absolutely certain whether any serum or solution containing horse antigens was ever given previously and whether there is any history of allergy, either in the patient or in any member of his family.

When any of these factors are present or if the reaction to the intradermal sensitivity test is positive, the serum must be administered carefully, as follows: The first dose should be 0.1 cc. administered subcutaneously; the dose is to be doubled at twenty minute intervals until 1 cc. is reached, and then the remainder can be administered in one dose intramuscularly. However, if the serum is to be administered intravenously also, the first dose must be small, i. e. 0.1 cc. diluted with 10 cc. of physiologic solution of sodium chloride and administered slowly, 1 cc. per minute, and the same progression is to be followed as in the subcutaneous dosage. Hyposensitization as employed here was first used by Besredka and Steinhardt,[283] in 1907, and its modification by dilution and slow intravenous administration, by Friedberger and Mita,[284] in 1911. Besredka compared the procedure to adding water drop by drop to concentrated sulfuric acid, after which any amount can be added without producing any undue reaction. Should a reaction to the serum occur, the next dose must not be increased, and if need be the absorption can be retarded by the use of a tourniquet above the site of

281. Cowie, D. M.: Studies on the Incubation Period: I. Serum Disease, Am. J. Dis. Child. **7**:253 (April) 1914.

282. Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, J. Immunol. **9**:7 (Jan.) 1924.

283. Besredka, A., and Steinhardt, E.: De l'anaphylaxie et de l'anti-anaphylaxie vis-à-vis du serum de cheval, Ann. Inst. Pasteur **21**:117 (Feb. 25) 1907.

284. Friedberger, E., and Mita, S.: Ueber eine Methode, grössere Mengen artfremden Serums bei überempfindlichen Individuen zu injizieren, Deutsche med. Wchnschr. **38**:204 (Feb.) 1912.

the inoculation, as recommended by Cooke and elaborated on by Insley.[285] However, if the reaction is an anaphylactic shock, the full dose can be given either at once or in increasing amounts. This procedure is safe, for, as previously mentioned, the human being reacts the same as the experimental animal, i. e. appears to be refractory to further injection of the same antigen immediately after recovering from anaphylactic shock, and the more severe the shock, the more likely this will be the case, according to Besredka, Manwaring[286] and Coca. If the dose is too large, a reaction may occur, as noted in Blankenhorn's[287] patient, who could withstand 15 cc. of pneumococcus serum injected twice daily intravenously but went into anaphylactic shock when the amount was raised to 25 cc. However, he did not state whether this dose was repeated. Weil, in his extensive studies on anaphylaxis in the guinea pig and the dog, observed that if the sensitizing dose is small the anaphylactic dose necessary is likewise small and vice versa. When the sensitizing dose is known, the minimal dose can easily be determined for the guinea pig but not for the human being, for the minimal desensitizing dose for one group may be four times the fatal dose for another. He observed that on occasion an anaphylactic shock may occur in the guinea pig the next day after survival of a shock and that sometimes it is followed by death; this confirms Doerr's observation. He noted, moreover, that anaphylaxis may occur during hyposensitization; this has been observed also by Cooke and Battley.[288] In this series, anaphylaxis was not seen if the hyposensitization was carried out as described, except in 1 patient, who had a 4 plus reaction to the intradermal test and a positive reaction to the conjunctival test. This patient had a local reaction after the first injection and none after the second but broke out with generalized urticaria almost immediately after the third injection, which was intramuscular. Epinephrine controlled the rash, and half an hour later she was given the remaining dose of antitoxin without a reaction. There were also 4 cases of anaphylaxis which occurred after some sort of hyposensitization; there was 1 of severe anaphylaxis in a patient who, as previously mentioned, received 0.25 cc. for the initial dose, and there were 2 cases of mild and 1 case of moderate anaphylaxis in patients who received a first dose of 0.25 cc. of antitoxin

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285. Insley, S. W.: Shock Following Hypodermic Medication, J. A. M. A. **94**:765 (March 15) 1930.

286. Manwaring, W. H.: Serophysiologische Untersuchungen: I. Der physiologische Mechanismus des anaphylaktischen Schocks, Ztschr. f. Immunitätsforsch. u. exper. Therap. **8**:1 (Nov. 7) 1910.

287. Blankenhorn, M. A.: Anaphylactic Shock and Failure of Desensitization, J. A. M. A. **85**:325 (Aug. 1) 1925.

288. Battley, J. C. S.: Serum Reaction Following Desensitization, Arch. Pediat. **48**:338 (May) 1931.

subcutaneously without a reaction and the remainder intramuscularly in one dose an hour later.

There have been various methods used to decrease the incidence of serum sickness, but thus far none have proved effective. Netter [289] found calcium helpful, but its daily administration in doses of 15 to 45 grains (0.97 to 2.91 Gm.) for ten days to 24 patients proved a failure in my hands as well as in those of Ramirez,[290] Hallam,[291] Luchessi and Stein,[292] Hunt, and Cohen and Rudolph,[293] while Coca and associates [294] stated that its value is considerably overestimated. On the other hand, Levy [295] observed that only 29 per cent of 55 children had serum sickness if they had received a dose of ephedrine before the injection of serum and then every eight hours for the next four days, while in 79 per cent of 43 children serum sickness developed if ephedrine was not given or was given irregularly. Luchessi and Stein did not see any benefit from this mode of therapy. Kraus,[296] on the other hand, seldom found serum sickness after the use of bovine serum. According to Wells,[297] the low incidence is due to the fact that beef is common in the diet, for he demonstrated that if guinea pigs were fed on certain vegetable proteins they could be anaphylactized but that if given an ordinary diet they could not be. Recently Foshay and Hagebusch,[298] followed by Cherry and Prickman,[299] claimed to have observed favorable results both in preven-

289. Netter, A.: Efficacité de l'ingestion de chlorure de calcium comme moyen préventif des éruptions consécutives aux injections de sérum, Compt. rend. Soc. de biol. **60**:279 (Feb. 10) 1906.

290. Ramirez, M. A.: The Value of Calcium in Asthma, Hay Fever and Urticaria, J. Allergy **1**:283 (March) 1930.

291. Hallam, R.: Remarks on Urticaria: Its Pathogenesis and Etiology, Brit. M. J. **2**:879 (Nov. 17) 1928.

292. Luchessi, P. F., and Stein, B. B.: Comparison of Therapeutic Agent in Treatment of Scarlet Fever, Pennsylvania M. J. **44**:162 (Nov.) 1940.

293. Cohen, M. B., and Rudolph, J. A.: A Clinical Study of the Use of Calcium in Controlled Cases of Allergy, J. Allergy **2**:34 (Nov.) 1930.

294. Coca, A. F.; Walzer, M., and Thommen, A. A.: Asthma and Hay Fever, Springfield, Ill., Charles C. Thomas, Publisher, 1931.

295. Levy, P.: Sur une méthode simple et efficace de prévention des accidents sériques au moyen de l'ingestion d'éphédrine, Bull. Acad. de méd. de Paris **109**: 711 (May 23) 1933.

296. Kraus, R.: Ueber die Verhütung der Serumkrankheit durch Anwendung des Diphtherie und Tetanusserums von immunisierten Rindern, München. med. Wchnschr. **69**:204 (Feb. 10); 1566 (Nov. 10) 1922.

297. Wells.[50] Wells, H. G., and Osborne, T. B.: The Biological Reactions of the Vegetable Proteins, J. Infect. Dis. **8**:66 (Jan.) 1911.

298. Foshay, L., and Hagebusch, O. E.: Histaminase in Treatment of Serum Sickness, J. A. M. A. **112**:2398 (June 10) 1939.

299. Cherry, J. H., and Prickman, L. E.: Treatment and Prevention of Serum Sickness by Use of Histaminase, Proc. Staff Meet., Mayo Clin. **16**:38 (Jan.) 1941.

tion and in treatment of serum sickness by using the enzyme histaminase. The number of cases of Foshay and Hagebusch is exceedingly small, and the results are not in the least convincing. One can readily appreciate the danger of drawing conclusions from their report when one glances at tables 26 and 32, which show the duration of serum sickness

TABLE 32.—*Average Duration of Serum Sickness* *

Serum	Negro	White
Diphtheria	2.8	2.3
Scarlet fever	2.8	2.6
Meningococcus	1.3	2.3
Scarlet fever and diphtheria	3.3	2.1
Poliomyelitis	...	2.5
Tetanus	...	2.6
Scarlet fever and meningococcus	...	2.0

* Days.

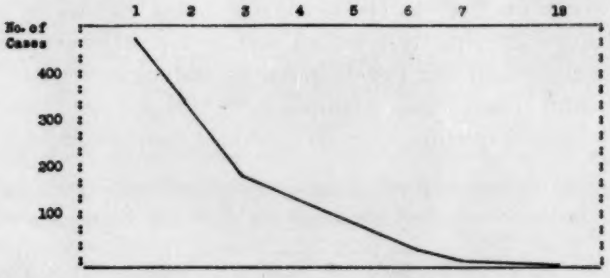

Chart 7.—Duration of serum sickness (days).

in this series, and perceives that the average duration was only slightly over two days, while in over one third of the cases, or 464, the duration was but a day or less.

However, the greatest advance in the reduction of serum sickness has been the proteolytic digestion of the serum by pepsin as prepared by Parfentjev.[300] With this serum, the incidence of serum sickness following the administration of scarlet fever serum in 318 cases in 1940 was just 4.4 per cent, compared with an incidence of 46 per cent in 118 cases during the same period in which a serum prepared the old way was used. Similar findings were reported by Baird,[301] Bradshaw,[302]

300. Parfentjev, I. A.: United States Patents 2065196 and 2123198, 1936. Weil, A. J.; Parfentjev, I. A., and Bowman, K. L.: Antigenic Qualities of Antitoxins, J. Immunol. **35**:399 (Nov.) 1938.

301. Baird, J. S., in discussion on Luchessi, P. F.: Worthwhile Immunization Procedures, Pennsylvania M. J. **42**:524 (Feb.) 1939.

302. Bradshaw, D. B.: New Serum in Passive Control of Scarlet Fever, Lancet **2**:6 (July 1) 1939.

Toomey and Kimball,[303] Hutchinson,[304] Arlt [305] and Top and Watson.[306] The serum sickness following the use of scarlet fever serum was mild, and anaphylaxis was not seen. The absence of anaphylaxis may have been due to a certain extent to the paucity of secondary injections but was probably chiefly due to the despeciation of the protein molecule. This was previously accomplished by Landsteiner, followed by Bronfenbrenner,[307] and, recently, by Coghill and associates,[308] using taka diastase. The serum prepared by Coghill and associates has been effective in inhibiting anaphylaxis in the guinea pig but as yet has not been given a trial in man.

There are a multitude of things which influence anaphylaxis, but only a brief outline can be given here; for a more complete summary, the articles of Longcope [309] and Isaacs [310] should be consulted. Anaphylaxis can be inhibited actively by repeated injections of the specific antigen [286] and passively by immune serum [311] and by various nonspecific agents. Species and family differences have been seen by most investigators and even age differences by some, as Thomsen [312] observed that young and old guinea pigs were harder to anaphylactize. White rats, which are ordinarily difficult to sensitize, can be readily sensitized if fed a deficient diet, especially one deficient in vitamin B_1.[313] Karady and associates [314]

303. Toomey, J. A., and Kimball, E. R., Jr.: Treatment of Scarlet Fever with Specific Antitoxins of Low Protein Content, J. Pediat. **15**:238 (Aug.) 1939.

304. Hutchinson, A.: Treatment of Diphtheria with Refined Antitoxin, Brit. M. J. **1**:384 (Feb. 25) 1939.

305. Arlt, H. G.: Diphtherie Fermoeserum, München. med. Wchnschr. **87**: 696 (June 28) 1940.

306. Top, F. H., and Watson, E. H.: Reduction of Serum Reactions: Use of Antitoxins of Which the Protein Specificity Has Been Altered by Enzymic Digestion, Am. J. Dis. Child. **62**:548 (Sept.) 1941.

307. Bronfenbrenner, J.: A Useful Modification in the Preparation of Therapeutic Sera, Proc. Soc. Exper. Biol. & Med. **27**:734 (May) 1930. Bronfenbrenner, J.; Hetler, D. M., and Eagle, I. O.: Modifications of Therapeutic Sera with a View of Avoiding Complications of Allergic Nature, Science **73**:455 (April 24) 1931.

308. Coghill, R. D.; Fell, N.; Creighton, M., and Brown, G.: The Elimination of Horse Serum Specificity from Antitoxins, J. Immunol. **39**:207 (Sept.) 1940.

309. Longcope, W. T.: Anti-Anaphylaxis and Desensitization, Physiol. Rev. **3**:240 (April) 1923.

310. Isaacs, M. L.: Nonspecific Desensitization, Arch. Path. **5**:1028 (June) 1928.

311. Manwaring.[286] Weil.[265]

312. Thomsen, O.: Studien über die Anaphylaxie (Antianaphylaxie), Ztschr. f. Immunitätsforsch. u. exper. Therap. **26**:213 (May) 1917.

313. Parker, J. T., and Parker, F., Jr.: Anaphylaxis in White Rat, J. M. Research **44**:263 (March) 1924.

314. Karady, I.; Selye, H., and Browne, J. S. L.: The Influence of the Alarm Reaction on the Development of Anaphylactic Shock, J. Immunol. **35**:335 (Nov.) 1938.

prevented anaphylaxis by placing guinea pigs in a temperature of 1 C. or by revolving them in a cage or by the administration of formaldehyde, while de Kruif and associate [315] prevented anaphylaxis by raising the temperature of guinea pigs to 109 or 110 F. In this investigation, fever did not appear to play any role, for every patient with anaphylaxis except 1 had fever; 1 who died had a temperature as high as 106 F. Endocrine influence also was demonstrated by Molomut [316] in hypophysectomized, and by Lanzenberg and Kepinow [317] in adrenalectomized, animals, since they are more readily shocked.

Pfeiffer and Mita [318] observed that if they injected normal beef serum into guinea pigs the animals could withstand a lethal dose of the specific antigen. This was further confirmed by Lewis,[319] in 1915, and more extensively by Kelloway and Cowell,[320] in 1922; the latter claimed that any normal serum would desensitize guinea pigs. They said that the reaction began in about fifteen minutes and reached its maximum in about an hour. Karsner and Ecker [321] found that by this means anaphylactic shock was inhibited but not completely prevented. In 1 of the cases in this series a transfusion of 250 cc. was followed seventeen minutes later by anaphylactic shock and death after 1 cc. of scarlet fever serum was administered intravenously, showing that this method is not effective in human beings, unless possibly the interval here was too short. Karady and Browne [322] claimed to have prevented anaphylaxis in the guinea pig by pretreatment with histaminase, but their finding could not be confirmed by Knoll,[323] Alexander and Bottom [324] and Youngner and associates.[325]

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315. de Kruif, P., and Simpson, W. M.: Possible Significance of Inhibitory Effect of Fever on Anaphylactic Phenomena, J. Lab. & Clin. Med. **26**:125 (Oct.) 1940.

316. Molomut, N.: The Effect of Hypophysectomy on Immunity and Hypersensitivity in Rats with a Brief Description of the Operative Technic, J. Immunol. **37**:113 (Aug.) 1939.

317. Lanzenberg, A., and Kepinow, L.: Glande thyroïde et anaphylaxie, Compt. rend. Soc. de biol. **86**:204, 1922.

318. Pfeiffer, H., and Mita, S.: Studien über Eiweiss-Anaphylaxie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **4**:410 (Jan.) 1910.

319. Lewis, J. H.: The Inhibitory Action of Heterologous Protein Mixtures on Anaphylaxis, J. Infect. Dis. **17**:241 (July) 1915.

320. Kelloway, C. H., and Cowell, S. J.: Non-Specific Desensitization, Brit. J. Exper. Path. **3**:268 (Dec.) 1922.

321. Karsner, H. T., and Ecker, E. E.: Specificity of Desensitized State in Serum Anaphylaxis, J. Infect. Dis. **30**:333 (March) 1922.

322. Karady, S., and Browne, J. S. L.: Effect of Histaminase Treatment on Histamine and Anaphylactic Shock in Guinea Pigs, J. Immunol. **37**:463 (Nov.) 1939.

323. Knoll, A. F.: Ineffectiveness of Histaminase in Anaphylactic Shock in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **45**:606 (Nov.) 1940.

In this entire series, however, no great difficulty was encountered if hyposensitization was properly performed. All of the deaths occurred in patients who had received their serum in one dose, although 1 had received only 1 cc. of undiluted serum intravenously. Every one of these deaths happened after a secondary injection, 1 on the eighth day, 3 on the fifteenth day and 1 on the seventeenth day after the primary injection, which corresponds to the interval of greatest sensitivity in the experimental animal, signifying that the utmost care must be exercised in giving injections during this period, even if the reaction to a sensitivity test is negative. However, the probability exists that death may occur even in the first week, as Ziskind and Schattenberg [326] reported an anaphylactic death, with typical postmortem observations, on the sixth day after the intravenous injection of 2½ minims (0.15 cc.) of typhoid vaccine. Two of the patients who died had a positive reaction to the intradermal test, and 2 had a negative reaction, while in the fifth patient the reaction to the conjunctival test was negative but the intradermal test was not done. If these patients had received a preliminary small dose subcutaneously, say 0.25 cc. or less, and the remainder one hour later if no reaction occurred, it seems highly probable from the results obtained here that they would have survived. Some confirmation of this may be had from the work of Besredka, Weil, and Ratner and Gruehl,[327] who noted that sensitized guinea pigs survived subcutaneous or intraperitoneal injections but died if the antigen was given intravenously or intraspinally. The largest initial dose suggested is 0.25 cc., because that amount in 1 patient, who had the most markedly positive reactions to intradermal and conjunctival sensitivity tests, produced severe anaphylactic shock with recovery. Of course, I have no way of telling how systemically sensitive were the patients who died who had reacted negatively to the tests, but I should be inclined to judge that they were not any more sensitive, and probably less so, than the patient just mentioned. All this applies only in cases in which the antigen is given intramuscularly. If an intravenous injection is to be made, the

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324. Alexander, H. L., and Bottom, D.: Failure of Histaminase to Protect Guinea Pigs Against Histamine and Anaphylactic Shock, J. Immunol. **39**:457 (Dec.) 1940.

325. Youngner, J. S.; Freedman, S. I., and Nungester, W. J.: Failure of Histaminase to Prevent Anaphylactic or Histamine Shock in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **46**:187 (Jan.) 1941.

326. Ziskind, J., and Schattenberg, H. J.: Fatal Anaphylactic Shock in Man, Arch. Int. Med. **62**:813 (Nov.) 1938.

327. Ratner, B., and Gruehl, H. L.: Investigations of Methods in the Study of Anaphylaxis, Proc. Soc. Exper. Biol. & Med. **26**:197 (Dec.) 1928.

method must be the same as that outlined for persons with a positive reaction to the sensitivity test.

Epinephrine, which up to the present time has been found to be the most valuable weapon in inhibiting as well as in treating anaphylaxis, was not given prior to the serum in any of the cases, but I favor the administration of 5 minims (0.3 cc.) of a 1 : 1,000 solution of epinephrine hydrochloride not only to every patient who gives a positive reaction to a sensitivity test or has received serum before or has a history of allergy but to every patient before receiving serum, irrespective of these factors. The fear of masking an oncoming reaction with this procedure may represent a definite probability, as Swineford and Grove observed that on the administration of epinephrine a 1 plus cutaneous reaction was made to disappear and a 2, 3 or 4 plus reaction was proportionately decreased in intensity. Nevertheless, I am of the opinion that if a severe reaction should be precipitated the likelihood of its control would not be made more difficult but, if anything, would be facilitated. Unquestionably, in the 5 cases of deaths reported here the bronchospasm, the hepatovenous spasm and the arteriospasm must have been so firmly established that they were not amenable to therapy, but, notwithstanding, the possibility remains that if treatment had been instituted before the injection of serum some muscular relaxation might have been produced and the condition simultaneously made more receptive to any subsequent therapy.

TREATMENT

Urticaria, unless severe, was easily controlled with calamine lotion containing 2 per cent phenol. However, not infrequently this failed to relieve the pruritus, and ephedrine hydrochloride (⅜ grain [0.025 Gm.]), orally, or 1 : 1,000 epinephrine hydrochloride solution (5 minims [0.3 cc.]), subcutaneously, had to be administered. When epinephrine was administered, the area was usually massaged gently for about a minute. Occasionally, epinephrine gave relief for only twenty minutes to half an hour, when another dose had to be given. On the other hand, there were 2 patients who apparently did not have any relief from this medication, and sedatives, even morphine, had to be resorted to. In 1 case morphine aggravated the pruritus and phenobarbital in doses of 5 grains (0.31 Gm.) had to be administered every six hours. In the majority of cases epinephrine controlled and relieved the pruritus in a few minutes. Ten units of insulin was used in 14 cases, with some benefit in 5. Stout and Kositchek [328] obtained dramatic results in all their 10 cases of urticaria associated with serum sickness by administering

328. Stout, M., and Kositchek, R. J.: Parenteral Use of Hypertonic Dextrose for Relief of Pruritus, Arch. Dermat. & Syph. **42**:802 (Nov.) 1940.

dextrose solution parenterally, while Curphey and Solomon [329] had some favorable results with parenterally administered calcium gluconate in 15 cases. The use of histaminase has already been mentioned under "Prevention."

The arthritis was not relieved readily by salicylates in doses of 10 grains (0.65 Gm.) by mouth, but great relief followed retention starch enemas containing 60 to 100 grains (4 to 6.5 Gm.) of sodium salicylate.

For nausea and emesis, tincture of belladonna in full doses, 0.25 cc., proved to be highly beneficial.

For the anaphylactic reactions epinephrine hydrochloride (5 minims [0.3 cc. of a 1 : 1,000 solution]) appeared to be a specific in almost all cases, except in the 5 listed fatal cases and in 1 other case in which epinephrine produced no response. If no response was obtained with 5 minims (0.3 cc.), larger doses of the epinephrine hydrochloride solution, even 1 cc. intracardially, proved valueless. For example, 1 child received 10 minims (0.6 cc.) with some benefit, but a few minutes later she began to tremble and her face and extremities became pale, and she was given another injection of 10 minims, which obviously only aggravated the existing symptoms. The patient was given whisky and soon appeared to be more comfortable. Three patients with epinephrine intoxication were treated with whisky with apparently some benefit. One of these patients described her symptoms as fear of impending death and a choking and a pressure sensation in the chest, probably due to pulmonary edema.[330] In this regard, a warning may be sounded that epinephrine intoxication may at times prove fatal, as reported by Gormsen.[331] If epinephrine failed to produce a response, atropine sulfate (1/300 to 1/50 grain [0.2 to 1.2 mg.]) or amyl nitrite had no apparent effect. Amyl nitrite was used because Drinker and Bronfenbrenner [332] observed that in rabbits suffering from anaphylactic shock the pulmonary pressure was increased for about twenty minutes and that this readily responded to administration of nitrites. Cooke also observed no beneficial effects of the administration of atropine and stated that occasionally in acute dilatation of the heart, it would prove a hazard if strophanthin or digitalis had to be administered.

329. Curphey, T. J., and Solomon, S.: The Therapeutic Value of Calcium Salts in Serum Sickness, New England J. Med. **214**:150 (Jan. 23) 1936.

330. Biedl, A.: The Internal Secretory Organs, New York, William Wood & Company, 1913. Selye, H.: Prevention of Adrenalin Lung Edema by Alarm Reaction, Am. J. Physiol. **122**:347 (May) 1938.

331. Gormsen, H.: Case of Fatal Epinephrine Intoxication, Ugesk. f. læger **101**:242 (Feb. 23) 1939.

332. Drinker, C. K., and Bronfenbrenner, J.: The Pulmonary Circulation in Anaphylactic Shock, J. Immunol. **9**:387 (Sept.) 1924.

In this series there were only 3 patients having spontaneous sensitivity, and every one was successfully given horse serum. This is rather a small number from which to draw final conclusions, but I believe that with patience and proper hyposensitization the majority, if not all, patients with spontaneous sensitivity can be successfully hyposensitized.

Thermal Reaction.—The treatment of thermal reaction, in order to be effective, had to be heroic and done with promptitude, for, as previously reported by me,[333] milder measures proved useless. For example, a boy 9 years of age with a temperature of 103.6 F. was given 5,000 units of scarlet fever serum intravenously; this was followed in a half-hour by a severe chill and a temperature of 108 F. The continuous use of alcohol sponges, an ice cap and salicylates did not reduce the fever. As a matter of fact, the temperature rose to 109 F. and the boy died in about an hour. I was greatly astonished to see this death, because prior to the administration of the serum the patient appeared acutely but not gravely ill, and I entertained the belief that the direct cause of death was not a toxemia associated with the disease but the induced hyperpyrexia. As a result, I decided in the future to treat these thermal reactions with an ice water colonic irrigation. There were 22 patients with a high thermal reaction on whom this mode of therapy was used. If it was instituted immediately after the onset of the fever, the result was gratifying in every case. However, if this treatment was instituted an hour after the onset of the hyperpyrexia, it proved unsuccessful. For example, a girl 4 years of age with a temperature of 104 F. was given 5,000 units of scarlet fever serum intravenously. An hour after the administration of the serum, she had a chill and became comatose and cyanotic. The temperature taken an hour after the chill was found to be 108 F. The pupils were dilated and did not react to light. Ice water colonic irrigation was given immediately, but the temperature did not drop until the clyster was used continuously for seventy minutes, when the temperature came down to 104 F. in the axilla. At this time, the pupils reacted to light, but the patient was still comatose. Three and a half hours later, she uttered a cry but appeared dull. An hour and a half later, the facies was still dull and the temperature was 102 F. Then the patient died. Necropsy showed congestion of the kidneys, the liver and the spleen. The adrenals were normal, and a blood culture was negative. However, stupor per se does not necessarily imply that the patient will not recover. For example, a boy of 3 years became stuporous after a thermal reaction of 107.2 F. There was a good response to promptly instituted therapy except for the stupor, which persisted for one week, when he became and remained alert.

333. Kojis, F. G.: High Human Temperature, J. A. M. A. **110**:1127 (April 2) 1938.

When the temperature reached 107 F. or over, the patients began to feel slightly delirious. However, in children convulsions were not infrequently seen when the temperature reached 106 F. Thermal reactions occurred fifteen to seventy-five minutes after the administration of the serum and were usually preceded by a chill, but not always. Witness the following case:

A 21 year old woman with scarlet fever came into the hospital appearing acutely ill, having a temperature of 105 F. She was given 5,000 units of scarlet fever serum intravenously, after having given negative reactions to conjunctival and intradermal sensitivity tests with horse serum. She had no chill, but about an hour later, on being asked how she felt, she replied, "I see angels." The temperature was taken immediately and found to be 110 F. Colonic irrigation with ice water was instituted, and the temperature came down to 104 F. in a half-hour. The next morning the temperature was normal, and it remained normal throughout her entire convalescence.

Thus in order to detect the onset of a thermal reaction, the safest procedure is to take the temperature every half-hour for an hour and a half and oftener if a chill occurs or some other adventitious sign, such as restlessness, convulsion, delirium or the complaint of feeling hot, makes its appearance.

Among the 6,211 patients treated with serum, there were 6 deaths directly due to thermal reactions. This number exceeded by 1 the total number of anaphylactic deaths. Similar deaths were observed by Conner,[334] Cecil and Larsen[335] and Lord and Heffron[336] after the use of antipneumococcus serum and by Toomey and Dolch and Banks after the use of scarlet fever serum. However, high thermal reaction may occasionally be seen after any infusion and may even be followed by death, as in the case reported by Kojis and McCabe,[337] in which 1,000 cc. of 5 per cent dextrose solution was given.

COMMENT

Coca stated that anaphylaxis in man has not been proved. Three of the patients in this series, who died within a minute to two hours after serum was intravenously administered, demonstrated the classic animal anaphylaxis, namely, sensitization, the interval for developing

334. Conner, L. A.: Experience in New York Hospital with the Treatment of Lobar Pneumonia by a Serum Free Solution of Pneumococcus Antibodies, Am. J. M. Sc. **164**:832 (Dec.) 1922.

335. Cecil, R., and Larsen, N. P.: Clinical and Bacteriological Study of One Thousand Cases of Lobar Pneumonia, J. A. M. A. **79**:343 (July 29) 1922.

336. Lord, F. T., and Heffron, R.: Pneumonia and Serum Therapy, New York, Commonwealth Fund, Division of Publications, 1938.

337. Kojis, F. G., and McCabe, E. J.: Primary Peritonitis Complicating Scarlet Fever, Am. J. M. Sc. **185**:710 (May) 1933.

sensitization and the reinjection followed by death with typical postmortem changes similar to those in the experimental animal. The other 2 patients, who died nine and a half and fifteen hours after receiving their secondary injections intramuscularly, presented symptoms similar to, if not identical with, those found in rabbits dying in prolonged anaphylaxis.[34] In addition, passive sensitization was demonstrated in 1 patient. Moreover, in 2 patients the refractory, or antianaphylactic, stage was seen after their recovery from anaphylactic shock. Similar observations were made by Gillette,[338] Patrick,[339] Alexander[340] and Thomas.[341] There are also cases on record, reported by Gillette, De Besche[342] and others, in which there was freedom from asthmatic attack lasting three months to three years after surviving anaphylactic shock.

The question may be raised: Why do not all of the patients die after repeated injections even if the interval corresponds to the maximum sensitivity? The argument defeats its own purpose, because all animals do not die after repeated injections; this has been the experience of all investigators from Magendie down to the present time. The other objection is: How are deaths following the primary injection to be accounted for? As the record shows, many of these patients had asthma or some other chronic respiratory disease; in not a few cases the history was incomplete, and in the majority the family history was overlooked. In addition, there must be considered the factor of unknown sensitization, as through inhalation, which was first so clearly demonstrated in guinea pigs by Ratner, Jackson and Gruehl[343] and later by Forster,[344] or through ingestion of horse meat, as Rosenau and Anderson proved that guinea pigs could then be anaphylactized, while Richet produced a similar response by feeding dogs with crepetin. Moreover, Kolle and Hetsch[345] found serum sickness was much more severe and much

338. Gillette, H. F.: Diphtheria Antitoxin and Bronchial Asthma, J. A. M. A. **50**:40 (Jan. 4) 1908.

339. Patrick, C. A.: Anaphylactic Shock After Injection of Serum Intravenously, Brit. M. J. **2**:114 (July 28) 1917.

340. Alexander, H. L.: Asthma Complicating the Serum Treatment of Pneumonia, Arch. Int. Med. **20**:636 (Oct.) 1917.

341. Thomas, H., Jr.: Pneumonia Type I Vegetative Endocarditis, Bull. Johns Hopkins Hosp. **31**:417 (Nov.) 1920.

342. De Besche, A.: Studies on the Reaction of Asthmatics and on Passive Transference of Hypersusceptibility, Am. J. M. Sc. **166**:265 (Aug.) 1923.

343. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Respiratory Anaphylaxis: Sensitization, Shock, Bronchial Asthma and Death Induced in a Guinea Pig by Nasal Inhalation of Dry Horse Dander, Am. J. Dis. Child. **34**:23 (July) 1927.

344. Forster, G. F.: Is There an Immunological Relationship Between Horse Serum and Horse Dander? J. Exper. Med. **47**:903 (June) 1928.

345. Kolle, W., and Hetsch, H.: Experimental Bacteriology, London, translated by D. Eriksen, Allen & Unwin, 1934, vol. 1, p. 175.

more frequent after the primary injection of horse serum into children who were fed on mare's milk, while Bernard, Debré and Porak [346] noted that anaphylaxis and death following the use of antituberculosis serum usually occurred only in hippophagi. Furthermore, the not infrequent presence of Forssman's heterophile antibody, as suggested by Taniguchi,[347] must be considered. The objection that a spontaneous allergic condition cannot be passively transferred remains to be seen, although the patient of Ramirez [348] had attacks of asthma in the presence of horse dandruff as well as a positive skin test to dandruff two weeks after receiving a transfusion from a donor with horse asthma. This, as Coca quoted, may have been a coincidence, but the sensitivity to strawberries [349] also was transferred by transfusion and lasted for four months, and rabbit hair sensitivity was passively transferred by Frugoni,[350] while pollen sensitization has been produced by Parker.[351] Thus, it is seen that man follows the pattern of the experimental animal in anaphylaxis and that there should be no doubt that this phenomenon does occur in man.

SUMMARY AND CONCLUSIONS

Various factors were observed to have an influence on the incidence of serum sickness and anaphylaxis, namely, the kind of serum, the preparation of serum, the quantity administered, the horse producing the serum, the race of the patient, the route of administration, repeated injections and the patient. The most important factors influencing the incidence of serum sickness were the kind and the preparation of serum, repeated injections and the patient.

When the reaction to the intradermal sensitivity test was positive, the incidence of serum sickness following inoculation with diphtheria antitoxin was four times, of anaphylaxis thirty-five times and of death mortality eleven times greater than when the reaction to the test was negative. If the reaction to the conjunctival test was positive, the incidence of serum sickness was five times and of anaphylaxis one hundred and seventy-three times greater.

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346. Bernard, L.; Debré, R., and Porak, R.: Sur la présence dans le sang circulant de l'albumine hétérogène après l'ingestion de viande crue, J. de physiol. et de path. gén. **14**:971, 1912; Sur le mécanisme et la prévention des accidents de la sérothérapie antituberculeuse, Presse méd. **20**:809 (Oct. 5) 1912.

347. Taniguchi, T.: Studies on Heterophile Antigen and Antibody, J. Path. & Bact. **25**:77 (Jan.) 1922.

348. Ramirez, M. H.: Horse Serum Asthma Following Blood Transfusion, J. A. M. A. **73**:984 (Sept. 27) 1919.

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If the reaction to the sensitivity test was positive, the incidence of serum sickness following inoculation with scarlet fever serum was 63 per cent higher, and that of anaphylaxis was thirty-three times higher than if the reaction to the test was negative. Comparison of the mortality rates was precluded by the lack of deaths in the patients who reacted negatively to the test.

Secondary injections of diphtheria antitoxin increased the incidence of serum sickness by 50 per cent, while the anaphylaxis rate was twenty-three times greater than after the primary injections. Use of the intramuscular route increased the incidence of anaphylaxis fourteen times, while use of the intravenous route increased it sixty-two times. Secondary injections of scarlet fever serum had no pronounced effect on the incidence of serum sickness, but the anaphylaxis rate was eight times greater than after the primary injection. Use of the intramuscular route increased the incidence of anaphylaxis three and a half times, while use of the intravenous route increased it twenty-two times. The 5 deaths which occurred all followed secondary injections, namely, 1 on the eighth day, 3 on the fifteenth day and 1 on the seventeenth day.

The incidence of seven different types of serum rashes is given, as well as the incidence of twenty-four different symptoms and signs.

Hyposensitization was found to be successful in 3 patients with spontaneous sensitivity, 1 with sensitivity to horse asthma, 1 to hay fever and 1 to hives.

Serum sickness with its protean manifestations must always be kept in mind when serum has been administered, in order to prevent embarrassing moments, complications and deaths.

The 5 deaths, each following a secondary injection, together with their symptoms and the typical postmortem observations in 2 cases, identical with those of experimental animals, demonstrate that anaphylaxis does occur in man. This is further substantiated by the refractory stage exhibited in 2 cases as well as by the passive transfer sensitization in 1.

The prevention, the treatment and the mechanism of serum sickness and anaphylaxis are discussed.

Thermal reactions were found to be dependent on the horse producing the serum.

Thermal reactions were decreased 50 per cent by fractional dosage.

The temperature must be taken at least every half-hour for one and a half hours or oftener if necessary after intravenous administration of serum or after any infusion.

High thermal reactions must be treated heroically with promptitude.

Sensitivity tests merit respect.

133 East Fifty-Eighth Street.

Obituaries

JAMES DOWLING TRASK, M.D.
1890-1942

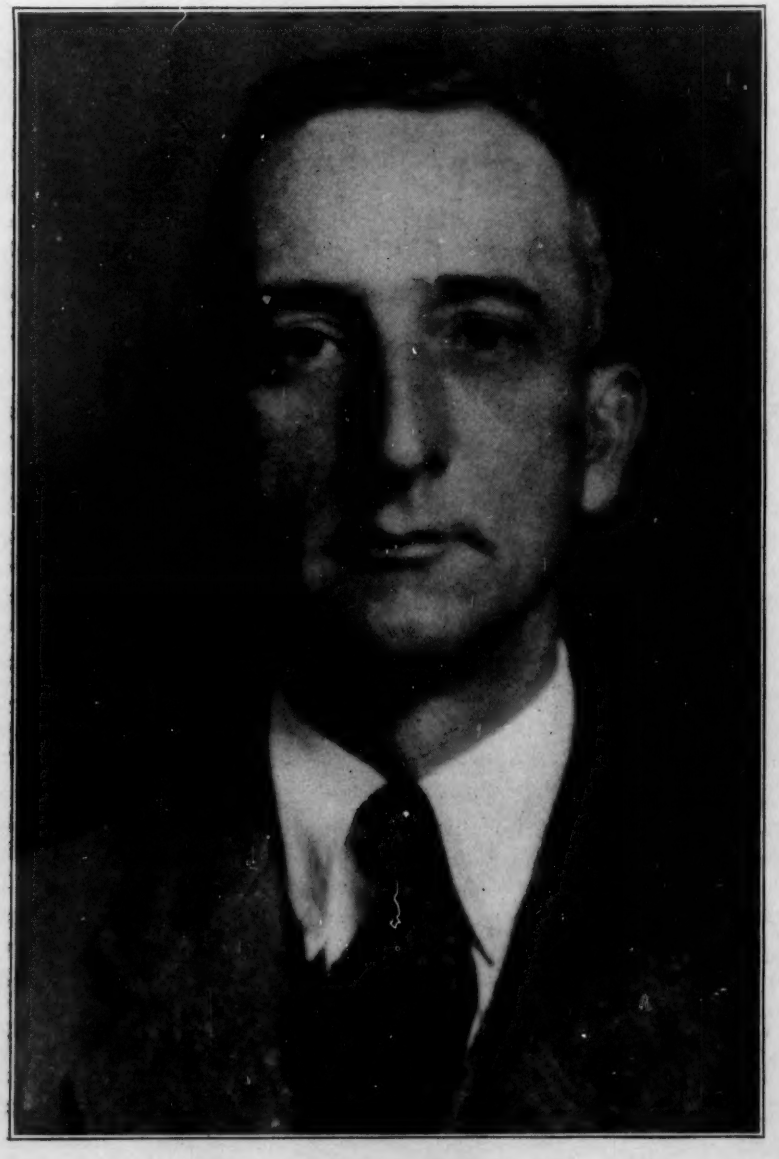
James Dowling Trask, son and grandson of physicians bearing that honored name, died May 24, 1942 in the Albert Merritt Billings Hospital, Chicago, of septicemia and peritonitis; he was ill only forty-eight hours.

Dr. Trask, though not commissioned in the armed forces, was nevertheless serving his country directly at the time of his death. In 1941 he became consultant to the Secretary of War as a member of the Commission on Neurotropic Virus Diseases and of the Commission on Hemolytic Streptococcal Infections; these commissions are attached to the Office of the Surgeon General of the Army. That his opinions were widely respected in the field of infectious diseases is shown by the fact that he had been asked to serve on four government commissions concerned with the prevention of epidemic diseases in the United States Army. Of these he chose two, giving his time during the summer to studies on poliomyelitis and other neurotropic virus diseases and during the winter to investigations of streptococcic infections. It was in connection with the latter work, with special reference to rheumatic fever, that he was taken with the fatal illness in the barracks at Chanute Field, Ill.; he is the first member of the Yale Medical Faculty to die while serving the armed forces of his country during this war.

Born Aug. 21, 1890, in Astoria, Long Island, James Trask took his baccalaureate degree (Ph.B.) at Yale University in 1913 and his medical degree at Cornell University Medical College in 1917. His graduate training was received at Bellevue Hospital and at the Hospital of the Rockefeller Institute for Medical Research. He was a first lieutenant of the Medical Corps, United States Army, from May 20 to Dec. 10, 1918.

Dr. Trask came to the Yale University School of Medicine in 1921. For the first six years of his association with the school he was a member of the department of internal medicine; during the last fifteen years he was associate professor of pediatrics and associate pediatrician to the New Haven Hospital.

In the latter period, Dr. Trask developed an infectious disease service and a laboratory for clinical bacteriology which are unique in university pediatric clinics. As a pediatrician, Dr. Trask was competent and often brilliant in dealing with children with infectious



JAMES DOWLING TRASK, M.D.
1890–1942

diseases. He loved to teach in the intimacy and informality of a small group, especially on bacteriologic and immunologic procedures in clinical medicine.

Before entering pediatrics, Dr. Trask's investigative work dealt largely with measles and scarlet fever. His researches in pediatrics, with various collaborators, were concerned with exact bacteriologic diagnosis of pneumonia in children, emphasizing the special importance of cultures from nasal swabs; establishment of the role of Haemophilus influenzae (type B) in the causation of certain forms of laryngotracheitis with bacteremia; extension of knowledge of the great group of streptococcic diseases, with special interest in rheumatic fever and in the fibrinolysin test of Tillett and Garner. Trask contributed the first paper in the first issue of the Yale Journal of Biology and Medicine; the title is "Comparative Immunology in Pediatrics." Beginning with the epidemic of poliomyelitis in New Haven, Conn., in 1931, he developed a great interest in that disease and established with his colleagues the Yale Poliomyelitis Commission, which has been concerned with many investigations, chiefly experimental and epidemiologic. These studies won the silver medal at the Scientific Exhibit of the American Medical Association in 1940, and, on April 22, 1942, the John Phillips Memorial Award of the American College of Physicians.

In 1939 Dr. Trask was appointed a Commissioner of the Board of Health of New Haven—a post for which he was unusually well qualified because of his strong sense of responsible citizenship as well as his broad knowledge of infectious diseases and of epidemiology. He was an active member of many scientific societies.

Jim Trask's friends were all those persons of every walk in life who came within the wide orbit of his acquaintance. His was a colorful and charming personality; he was unique in his gifts of friendship and fine fellowship and delightfully stimulating in his many diverse interests. No one can think of him without recalling his love of Nature—the woods, the fields, the sea—a love which was but a part of his oft expressed pride and faith in his country, its vast developments, its expanding horizons in the search for truth. In that faith and in that search he lives on in the minds and hearts of those who enjoyed the high privilege of his comradeship in work and in play.

G. F. P.

BERNARD JEAN ANTONIN MARFAN, M.D.
1858-1942

Bernard Jean Antonin Marfan, born in 1858, died Feb. 11, 1942 in his native city, Castelnaudary, in what is now unoccupied France. He received his medical degree in Paris in 1887.

Marfan made many important contributions to pediatric literature. He was also a teacher of renown; his clinics were eagerly sought by students from France as well as from foreign lands.

His academic record began with his position as chief of the clinic at Hospital Wecker, where he served from 1889 to 1891. In 1892 he was appointed assistant professor on the Paris faculty, and in 1910 he became professor of therapeutics. When the newly founded chair of hygiene and the clinic of infantile diseases was established on the Paris faculty, he was named professor in 1914.

He wrote on many important subjects, some of which may be briefly mentioned: "On the Relation of Infantile Eczema to Errors in Feeding," 1894; "Typhoid Fever," 1894; "Tuberculous Peritonitis," 1894, and "Congenital Affections of the Newborn," 1897. Together with Charles Gillet, he published studies on oxidase and lipase of milk, and he was one of the co-editors with J. Grancher and J. Comby of "Traité des Maladies de l'Enfance," 1897. He made some interesting observations on goat milk feeding; he found no advantage in the direct suckling of infants by goats, a custom which has been in vogue for centuries in rural France. He also found that infants fed on goat's milk showed signs of rickets, became anemic and had distended abdomens.

In 1889 Marfan published a comprehensive treatise on "Infant Feeding and Nutrition." The book described various methods of feeding then in use and gave a detailed description of the physical and chemical properties of milk and of its bacterial count. The book also contained a chapter on metabolism, particularly a review of the metabolism of breast-nursed and artificially fed infants as well as of those who were suffering from malnutrition and intestinal intoxication. He was also the author of several books on pediatrics and the editor of the journal *Le Nourrisson.*

Marfan lived a long and useful life devoted to the advancement of pediatrics. He was one of the last of the rapidly disappearing group of pediatricians who aided in building pediatrics from its very foundations to an edifice which is now believed to have attained some magnitude.

In each department of medicine it is well for physicians to consider the contributions which their predecessors have made. They should concede that Marfan and his comtemporaries in many lands have bequeathed to them clinical data which serve a beneficient purpose to this day in the management and treatment of infants in health and in disease.

I. A. A.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

AN ADDITIONAL GROWTH FACTOR NEEDED BY SOME HEMOLYTIC STREPTOCOCCI. A. BASS, SAM BERKMAN and FELIX SAUNDERS, J. Infect. Dis. **68**:221 (May-June) 1941.

Some beta hemolytic streptococci fail to develop in the presence of the known growth factors which support ready growth of other streptococci. The addition of certain tissue extracts or of yeast supplies unknown substances needed by these more "fastidious" organisms.

Some sources of this unknown factor (or factors) are given, together with some of its physical and chemical properties. A procedure for preliminary purification is suggested.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

SULFAPYRIDINE RESISTANCE OF PNEUMOCOCCI FOLLOWING SULFAPYRIDINE THERAPY IN INFANTS AND CHILDREN AND THE COMPARATIVE POTENCY OF THREE CHEMOTHERAPEUTIC AGENTS FOR PNEUMOCOCCI AS SHOWN BY LABORATORY TESTS. W. J. AUGER, J. Pediat. **18**:162 (Feb.) 1941.

This paper is a description of a simple plate method by which the sensitivity to or resistance of pneumococci to sulfapyridine may be demonstrated. This method has been found suitable for comparing roughly in vitro the relative activity of various chemotherapeutic agents against pneumococci. The test was applied to cultures from 2 patients who did not respond to sulfapyridine. These cultures showed marked resistance to sulfapyridine, as compared with similar cultures from patients not receiving chemotherapy and with cultures obtained before administration of the drug to the same patients. In vitro tests demonstrated that sulfanilamide, sulfapyridine and sulfathiazole differed in the potency in which they prevented the colonial growth of pneumococci, sulfanilamide being the weakest and sulfathiazole the strongest.

RAUH, Cincinnati.

Metabolism; Infant Feeding; Milk and Other Foods

THE EFFECT OF SULFANILAMIDE ON ACID BASE BALANCE. E. W. MCCHESNEY, KIMBALL D. SPRAGUE and IRVINE H. MARSHALL, J. Lab. & Clin. Med. **26**:1154 (April) 1941.

Using dogs as the experimental animals, the authors came to the conclusion that the disturbance in acid-base balance is due to loss of alkali from the blood into the urine. The cause of this loss may be some type of interference with the reabsorption of bicarbonates from the glomerular filtrate. Assuming this conclusion to be correct, one may compensate for the loss by administering alkali.

GARD, Galveston, Texas.

METHOD FOR THE QUANTITATIVE ESTIMATION OF ACETONE AND ACETOACETIC ACIDS IN URINE. LORRAINE F. NOYES, J. Lab. & Clin. Med. **26**:1219 (April) 1941.

A simple and practical clinical method is described for the quantitative estimation of acetone and acetoacetic acid in urine. It is accurate when these substances are present in the urine to a pathologic degree.

GARD, Galveston, Texas.

DEPLETION OF TISSUE GLYCOGEN DURING FASTING AND FATIGUE AND PARTIAL RECOVERY WITHOUT FOOD. PAULINE E. NUTTER, J. Nutrition **21**:477 (May) 1941.

Nutter found more closely agreeing results in the glycogen content of paired muscles removed from rats anesthetized with amytal than in those from animals killed by a sudden blow on the head. She noted that the liver glycogen was reduced to a very low level by a twenty-four hour fasting period and to a slightly lower level by fatiguing exercise. While the muscle glycogen was reduced by one third by the fasting period, she observed that the rate of fall was much slower after the first twenty-four hours. Fatiguing exercise during fasting decreased the muscle glycogen content to a much lower level. In spite of the fasting state, a small amount of glycogenesis occurred during the recovery period after fatigue by swimming eight hours. The liver glycogen reached a level twice as high as that observed after fasting alone by the third hour of the recovery period; the muscle glycogen rose notably during the first two hours but only slightly during the third hour. FREDEEN, Kansas City, Mo.

GLYCOGEN FORMATION IN LIVER AND MUSCLE FROM GLUCOSE AND FRUCTOSE AFTER EXTREME MUSCULAR EXHAUSTION. PAULINE E. NUTTER and J. R. MURLIN, J. Nutrition **21**:489 (May) 1941.

Nutter and Murlin noted that fructose was absorbed at a much slower rate than dextrose by a fatigued rat, but both sugars showed a decreased rate of absorption as the time was prolonged. Dextrose was superior to fructose in liver glycogenesis during the first hour of the recovery period; however, fructose approached dextrose in activity during the second hour and was much more effective during the third hour. The difference between the two sugars in muscle glycogenesis was not statistically significant at any time.

FREDEEN, Kansas City, Mo.

THE DISTRIBUTION OF PYRIDOXINE (VITAMIN B_6) IN MEAT AND MEAT PRODUCTS. LAVELL M. HENDERSON, HARRY A. WAISMAN and C. A. ELVEHJEM, J. Nutrition **21**:589 (June) 1941.

Henderson, Waisman and Elvehjem present a table showing the pyridoxine content of meat and meat products as determined by means of the rat growth method. Kidney and muscle are the richest sources, with heart and liver about 50 per cent less, and spleen, pancreas, brain and lung the poor sources. The fried meats showed the least destruction, while roasting and stewing caused 20 to 50 per cent losses. FREDEEN, Kansas City, Mo.

STUDIES ON THE ABSORPTION, DISTRIBUTION AND ELIMINATION OF ALCOHOL. HOWARD W. HAGGARD, LEON A. GREENBERG and RICHARD P. CARROLL, J. Pharmacol. & Exper. Therap. **71**:349 (April) 1941.

Experiments were made on 12 men to determine some of the general factors determining the rate of elimination of alcohol in the urine. While alcohol is little used in pediatric practice, the conclusions of the authors are of much general interest. At a uniform rate of urinary secretion, the amount of alcohol eliminated in the urine varies approximately as the square of the amount ingested; the percentage of alcohol eliminated varies directly as the amount ingested. The greatest variation in the amount eliminated results from the diuresis caused by alcohol. There are wide individual differences in the extent of diuresis from alcohol. Ingredients of alcoholic beverages other than alcohol do not contribute to the diuresis. Diuresis occurs only when the concentration of alcohol in the blood is rising. It does not result from the mere presence of alcohol in the blood and does not occur when the concentration is stationary or falling. PILCHER, Cleveland.

STUDIES ON THE ABSORPTION, DISTRIBUTION AND ELIMINATION OF ALCOHOL: IX. THE CONCENTRATION OF ALCOHOL IN THE BLOOD CAUSING PRIMARY CARDIAC FAILURE. H. W. HAGGARD, L. A. GREENBERG, L. H. COHEN and N. RAKIETEN, J. Pharmacol. & Exper. Therap. **71**:358 (April) 1941.

The authors have previously shown that in normal rats the average concentration of blood alcohol causing respiratory failure is 9.31 mg. per cubic centimeter. When respiratory failure is prevented by artificial respiration, the average concentration of blood alcohol causing cardiac failure is 12.6 mg. per cubic centimeter. The main toxication of alcohol is on the myocardium. Cardiac failure is prevented by preventing anoxemia by means of artificial respiration.

PILCHER, Cleveland.

Vitamins, Avitaminoses

THE CALORIC INTAKE AND WEIGHT BALANCE OF HYPERTHYROID DOGS IN RELATION TO VITAMIN B_1 AND YEAST. VICTOR A. DRILL, Am. J. Physiol. **132**:169 (April) 1941.

The food intake of 6 dogs receiving a normal diet containing yeast increased to nearly twice the normal level when feeding of thyroid was started. After three to four weeks of thyroid feeding the food intake began to decline, indicating depletion of the stores of vitamin B in the body. When the yeast was removed from the diet of the hyperthyroid dogs, the appetite rapidly fell below normal, complete anorexia being produced in some cases. The subcutaneous injection of 2 mg. of thiamine hydrochloride restored the appetite to the previous hyperthyroid level within twenty-four to forty-eight hours.

The decrease in appetite of the dogs receiving thyroid is due to a deficiency of vitamin B_1. Anorexia is not a primary effect of hyperthyroidism but is a secondary symptom due to a deficiency of vitamin B_1. The weight of the hyperthyroid animals was maintained as long as no deficiency of the vitamin B complex occurred.

NOURSE, Cleveland.

THE EFFECT OF THIAMIN ON THE INTESTINE OF THE B. DEFICIENT RAT. DICK MACDONALD and J. ROY HEGE JR., Am. J. Physiol. **132**:636 (April) 1941.

It has frequently been observed that crude vitamin B products increase the intestinal motility of deficient animals. Observations made after the identification of thiamine as the antineuritic principle suggest that vitamin B_1 is the factor responsible for the effect.

The authors used a solution of thiamine hydrochloride to perfuse the intestines of normal rats and of rats which had been fed a diet deficient in vitamin B_1. No effect was noted in the normal animals. On the other hand, the peristalsis of the intestines of the rats deficient in vitamin B_1 was increased and the rate of tonus loss retarded within ten minutes after the addition of thiamine.

NOURSE, Cleveland.

THE SPARING ACTION OF THIAMINE ON BODY TISSUE CATABOLISM. BARNETT SURE and MAURICE DICHEK, J. Nutrition **21**:445 (May) 1941.

Sure and Dichek find from their work with rats that greater intakes of thiamine exert a sparing influence on the catabolism of body tissue during periods of inanition produced by a deficiency of this vitamin. It is suggested that this influence may be due to the effect of thiamine on intermediate carbohydrate metabolism.

FREDEEN, Kansas City, Mo.

RIBOFLAVIN AS A FACTOR IN ECONOMY OF FOOD UTILIZATION. BARNETT SURE, MAURICE DICHEK and MARTIN M. CITRON, J. Nutrition **21**:453 (May) 1941.

Sure, Dichek and Citron, in their rather extensive experimentation with rats, found that riboflavin produced a definite and great effect on economy of food utilization for the synthesis of body tissues. The increase in body gains was primarily derived from fats and to a lesser extent from protein.

FREDEEN, Kansas City, Mo.

VITAMIN A DEFICIENCY: A FIELD STUDY IN NEWFOUNDLAND AND LABRADOR. DAVID STEVEN and GEORGE WALD, J. Nutrition **21**:461 (May) 1941.

Steven and Wald made a rather extensive study and survey of the incidence of vitamin A deficiency in an area from which epidemic night blindness had been reported. They used a specially designed portable adaptometer to measure the visual threshold. They found that a rise of this threshold above "a normal range" was not indicative of a deficiency of vitamin A, but rather that deficiency is indicated by a "vitamin A–labile threshold—one that, whatever its initial level, is lowered at least 0.3 logarithmic unit within 2 weeks of regular vitamin A supplementation." However, in practice a threshold which reacted to vitamin A did so within one to six hours. Clinical night blindness was found in 3 per cent of the subjects and vitamin A–labile thresholds in 9.7 per cent. Approximately 50 per cent of the vitamin A–labile thresholds were within "normal range." About half were found in patients suffering from beriberi, but vitamin A–labile thresholds and beriberi were independent. However, in patients with both deficiencies brewers' yeast did not lower the threshold, while vitamin A alone was as effective as the two vitamins combined. The deficiencies were most prevalent in February and March, and both were found principally in adults. Beriberi occurred primarily in males of the average age of 40 years, while vitamin A deficiency was noted in both sexes at the average age of 26 years.

FREDEEN, Kansas City, Mo.

STUDIES ON THE VITAMIN C METABOLISM OF FOUR PRESCHOOL CHILDREN. MILICENT L. HATHAWAY and FRIEDA L. MEYER, J. Nutrition **21**:503 (May) 1941.

Hathaway and Meyer studied four preschool children on various levels of ascorbic acid intake with an otherwise constant diet. They found a daily intake of 31 mg. of ascorbic acid was the marginal level to insure tissue saturation in these 4 children. The "utilization" or percentage of retention was relatively constant. The average value was 23 $\pm$ 2 mg. at levels of intake from 31 to 50 mg.

FREDEEN, Kansas City, Mo.

A STUDY OF VITAMIN C NUTRITION IN A GROUP OF SCHOOL CHILDREN. ELIZABETH MURPHY, J. Nutrition **21**:527 (May) 1941.

Murphy studied a group of 86 elementary school children of French-Canadian extraction in a Maine village during the late fall of 1938 and early spring of 1939, seasons when the foods containing vitamin C were least abundant. From her analysis of 76 fall and 63 spring diet records, she found that only 1 child in 7 attained the minimum dietary standard of one good vitamin C food daily. The chief source of vitamin C in the dietaries observed was potatoes, and the ascorbic acid values of raw Green Mountain potatoes decreased from 0.17 mg. per gram in the fall to 0.11 mg. in the spring. Losses during cooking, according to the technics employed in this region, were considerable: for potatoes, 27 to 55 per cent; for cabbage, 46 to 67 per cent; for rutabagas, 14 to 50 per cent; for fiddlehead greens, 29 to 56 per cent. The findings of vitamin C undernutrition in 63 per cent of the children examined showed plasma ascorbic acid values of less than 0.40 mg. per hundred cubic centimeters, and 51 per cent of the children showed oral inflammation. Inadequate vitamin C intake was noted in 40 per cent of the dietaries examined.

FREDEEN, Kansas City, Mo.

THE URINARY EXCRETION OF THIAMIN IN NORMAL CHILDREN. REUEL A. BENSON, MICHAEL WITZBERGER and LAWRENCE B. SLOBODY, J. Pediat. **18**:617 (May) 1941.

The urinary excretion of thiamine of normal children ranged between 92 and 602 micrograms per day and averaged 268 micrograms. For children in this age and weight group, an intake of 45 micrograms (15 international units) of thiamine per hundred calories, or 990 micrograms (330 international units) daily, seemed adequate to provide for excellent health. The average amount of thiamine excreted was 27.2 per cent of the amount ingested. The morning determinations of thiamine in the urine do not furnish a constant ratio to the total twenty-four hour output. RAUH, Cincinnati [AUTHORS' SUMMARY].

AVITAMINOSIS A: INCIDENCE IN A GROUP OF ONE HUNDRED HOSPITALIZED CHILDREN AS MEASURED BY THE BIOPHOTOMETER. HOWARD G. RAPAPORT and DOROTHY GREENBERG, New York State J. Med. **41**:879 (April 15) 1941.

A study of vitamin A deficiency, as measured by the biophotometer on a group of 100 afebrile children from 6 to 13 years of age, is reported. Sixty per cent of the tests gave normal results and 11 per cent borderline, and 29 per cent showed a deficiency of vitamin A. AIKMAN, Rochester, N. Y.

ACTIVITY OF ALPHA TOCOPHEROL IN PREVENTING ANTAGONISM BETWEEN LINOLEIC AND LINOLENIC ESTERS AND CAROTENE. W. C. SHERMAN, Proc. Soc. Exper. Biol. & Med. **47**:199 (June) 1941.

Rats reared on a vitamin A–deficient diet were found to fail to grow if methyl esters of linoleic and linolenic acid were fed together with carotene or vitamin A. This antagonistic action of carotene and the methyl esters of these unsaturated fatty acids was prevented by the addition of soybean oil and alpha tocopherol. Soybean lecithin or cephalin, choline and ethanolamine had no such effect. From these experiments it appears that in the absence of alpha tocopherol there is a physiologic antagonism between unsaturated fatty acids and carotene which results in the inefficient utilization of carotene. HANSEN, Minneapolis.

SITE OF VITAMIN A STORAGE IN THE LIVER. ALVIN J. COX, Proc. Soc. Exper. Biol. & Med. **47**:333 (June) 1941.

Determination of the vitamin A content in various parts of the liver by the use of the Carr-Price antimony trichloride reaction in 3 cases of healed massive necrosis of the liver revealed this vitamin to be less abundant in the areas in which the hepatic cells had not been destroyed. Apparently the vitamin A was stored in the Kupffer cells. HANSEN, Minneapolis.

Hygiene, Growth and Nutrition; Public Health

FURTHER RESULTS ON THE TREND OF WEIGHT IN WHITE SCHOOL CHILDREN. GEORG WOLFF, Child Development **12**:183 (June) 1941.

The present report is the second of a series of studies dealing with annual variations in weight of white school children of Hagerstown, Md. The observational data of the four year period 1937 to 1940 comprise nearly 20,000 weight measurements, 10,059 of boys and 9,938 of girls. Together with 14,401 weight measurements taken in the preceding four year period, 1933 to 1936, the observations in the eight successive calendar years cover a total of around 34,400 measurements. There is a distinct secular upward trend in weight for all age groups and for both sexes, best to be realized when the averages of the two periods are compared. In boys the mean increase is statistically significant in the ages from 6 years (6-7) through 15 years (15-16); in girls it is beyond the limits of chance in the lowest age group, 6 to 7 years, and from 10 years of age and up. When

the combined values of the total period of eight years, 1933 to 1940, are compared with the values obtained by Palmer for a period in the previous decade, there is no essential variation in body weight of the young school children from 6 years up to 11 years of age, but again a significant increase in mean body weight of the older boys and girls. The phenomenon of a real increase of bodily dimensions is worldwide. As a possible explanation it is hinted that the growth phenomenon may be indirectly associated with the general decrease of births in the western world and the connected diminution in size of family. Such a bearing appears the more reasonable after it has become evident from new figures that the higher socioeconomic classes have during the last decades increased their proportional contribution to the natality of the population as a whole.

THE PRIVATE PHYSICIAN—AN IMPORTANT LINK IN SCHOOL MEDICAL SERVICE. JACOB H. LANDES, New York State J. Med. **41**:973 (May 1) 1941.

The private physician should be urged to cooperate in school medical supervision.

AIKMAN, Rochester, N. Y.

PHYSICAL EXAMINATION OF SCHOOL PERSONNEL. ELMER HARRISON ORMSBY, New York State J. Med. **41**:991 (May 1) 1941.

The physical and mental welfare of school personnel should be constantly under supervision.

AIKMAN, Rochester, N. Y.

VITAL CAPACITY AND PHYSICAL EDUCATION. VICTORIO V. OLGUIN, Rev. méd. latino-am. **26**:1007 (June) 1941.

This is a study of the effect of exercise on the vital capacity. A preliminary test of 550 military students, aged 11 to 20 years, showed the average capacity to be 3,700 cc. Toward the end of the school year the average was 3,880 cc. Only 259 students (49 per cent) increased their vital capacity, probably because most of the cadets had engaged in strenuous sports before entering military college.

DWYER, Kansas City, Mo.

Newborn

SKIN TESTING IN THE NEWBORN. BENJAMIN ZOHN, Arch. Pediat. **58**:339 (June) 1941.

In 150 infants 3 to 8 days of age who were treated with milk, egg and wheat no positive wheal reactions were obtained. Cutaneous tests with histamine performed on 25 infants elicited positive wheal reactions in every instance. Tests with irritating extracts, such as dust, wool and feathers, caused 3 equivocal positive wheal reactions to dust. Erythematous reactions occurred more frequently with these tests than when wheat, egg, milk and diluting fluid were used. The author concludes that definite evidence of sensitivity to foods at birth is still lacking.

ORR, Buffalo.

A COMPARISON OF ROUTINE HOSPITAL RECORDS OF BIRTH STATURE WITH MEASUREMENTS OF BIRTH STATURE OBTAINED FOR LONGITUDINAL RESEARCH. HOWARD V. MEREDITH and JACK L. GOODMAN, Child Development **12**:175 (June) 1941.

This study constitutes one unit of a pattern of research considered basic to the rigorous collection of seriatim data. Specifically, the aims of the study are: "1. To determine the reliability of stature measurements taken on newborn infants under reasonably optimum laboratory conditions. 2. To compare routine hospital records of birth stature with records derived from the reliability study. 3. To evaluate the research usefulness of routine hospital records."

The subjects were 100 white newborn infants born at Hospital X, Iowa. On reliability (with a carefully defined anthropometric technic and an experimental

procedure which gave independent measurements), it was found that the difference in s[illegible]e as obtained by two anthropometrists did not exceed 1 mm. for 48 (48 per cent) of the subjects and was 5 mm. or less for 92 per cent. The mean of the differences from the 100 paired values was 2.4 mm., the reliability coefficient (Pearson product-moment), 0.973.

From the reliability data, a single stature record was derived for each subject. Next the difference between this record and the corresponding hospital record for each subject was determined. For 46 per cent of the infants the difference was 10 mm. or more. The mean of the differences between the two series of records was 11.2 mm.; the correlation coefficient, 0.741.

Regarding the usefulness of routine hospital records in research, the investigators find these to be satisfactory if only a measure of central tendency is required but to be inadequate for use in studying variability, stature rank of the individual in the group or problems relating to individual growth during infancy.

EFFECT ON THE NEWBORN OF VITAMIN K ADMINISTERED TO MOTHERS IN LABOR. J. W. MULL, A. H. BILL and HELEN SKOWRONSKA, J. Lab. & Clin. Med. **26**:1305 (May) 1941.

This paper is based on a study of 100 women who were given vitamin K while in labor. The figures obtained for the prothrombin time of their infants are compared with the prothrombin time of infants whose mothers received no vitamin K. The authors find the average prothrombin time of the babies of the treated series to be much shorter than that of the controls. They used only 1 mg. of synthetic vitamin K (menadione) in corn oil, and feel that this is effective.

GARD, Galveston, Texas.

A SIMPLIFIED DETERMINATION OF BLOOD PROTHROMBIN LEVELS IN THE NEWBORN. CARL P. HUBER and JACK C. SHRADER, J. Lab. & Clin. Med. **26**:1379 (May) 1941.

Using a modification of the Smith bedside method for prothrombin times, the authors have studied the clotting activity of 114 babies. Their method for these determinations is relatively simple. The thromboplastic material is obtained from the lungs of either sheep or swine. The article contains graphs to show the variation in clotting activity of normal infants, but as a rule these curves are more or less typical. The lowest level occurs from forty-eight to seventy-two hours after birth, and then the level rises rapidly to the normal range.

GARD, Galveston, Texas.

THE EFFECTS OF ASPHYXIA ON THE NEWBORN INFANT. STEWARD H. CLIFFORD, J. Pediat. **18**:567 (May) 1941.

Eleven newborn infants who met asphyxial deaths have been studied. In all the fetal anoxemia was produced by the separation of a low attached placenta, accompanied by active hemorrhage just prior to birth. All the infants were delivered by cesarean section performed before the onset of labor. Clifford draws the following conclusions: Asphyxia is responsible for over one half of the deaths of live-born infants in the newborn period. The fundamental effect of asphyxia is the production of an increased hydrogen ion concentration, which causes the successive stages of stimulation, discharge of energy and paralysis in nerve cells and produces loss of tone and dilatation of the smooth muscle of blood vessels, allowing escape of plasma and red blood cells. The pathologic changes induced by asphyxia are congestion, edema, hemorrhage and tissue degeneration, and they may involve every organ and tissue of the body. The atelectasis of the lungs seen in asphyxiated infants may be due to a combination of factors: the normal resistance of expansion due to the cohesion of moist surfaces; injury to the respiratory center; bronchial obstruction and increased turgor of the lung tissue due to congestion; edema, and hemorrhage associated with asphyxia.

RAUH, Cincinnati.

FAVORABLE END RESULTS IN ICTERUS GRAVIS NEONATORUM. IRWIN PHILIP SOBEL, J. Pediat. **18**:621 (May) 1941.

Sobel reports 2 cases of icterus gravis neonatorum in patients who at the age of 6½ and 17 months respectively were in perfect physical and mental health and presented no abnormal neurologic signs. Icterus gravis neonatorum has so frequently had appalling neurologic sequelae as a result of of nuclear jaundice and intracranial hemorrhage that doubts have been cast on the permanent advantages of successful immediate therapy in cases of severe attacks of this disease. These 2 cases demonstrate that active therapy during the neonatal period is of real value, since apparently normal infants may be the reward of successful treatment. Sobel raises the question of the hereditary character of this disease and believes that as more healthy infants cured of icterus gravis reach a reproductive period it may be possible to test directly the hypothesis of the hereditary nature and of the mendelian transmission of this disease. RAUH, Cincinnati.

PROTHROMBIN IN THE NEWBORN INFANT: II. PROTHROMBIN RESPONSE TO WATER-SOLUBLE NAPHTHOQUINONE ADMINISTERED INTRAVENOUSLY; III. ON THE NATURE OF PROTHROMBIN IN THE NEWBORN INFANT. SIMON KOVE and HENRY SIEGEL, J. Pediat. **18**:764 (June) 1941.

Four newborn infants were chosen as representative of the various degrees of severity of hypoprothrombinemia. Detailed prothrombin studies were performed on the plasma of these infants at short intervals following intravenous administration of 1 mg. of menadione (2-methyl-1, 4-naphthoquinone). In all cases there was a definite prothrombin response within two hours after therapy. In the individual cases the interval from the time of administration of the menadione until the initial effect became apparent on the prothrombin level was found to vary from within one-half hour to two hours. In the infant with only moderate prothrombin deficiency the prothrombin level reached a normal value within eight hours, while those with severe deficiency were still somewhat hypoprothrombinemic at the end of this period. The nature of the prothrombin of the newborn infant was investigated to determine its similarity to that of the normal adult. This was accomplished by comparing the graphs of the prothrombin clotting times of serial dilutions of plasma of normal adults and of newborn infants under various conditions. The resulting curves for infants with normal prothrombin deficiency were similar to those of normal adults. A similar curve was obtained for a newborn infant whose prothrombin was produced as a result of menadione therapy. These similarities offer presumptive evidence that the prothrombin of the newborn infant is qualitatively similar to that of the normal adult, regardless of its concentration or source. RAUH, Cincinnati [AUTHORS' SUMMARY].

Acute Contagious Diseases

THE EPIDEMIOLOGY OF ANTERIOR POLIOMYELITIS. MARGARET BASHFORD, Arch. Pediat. **58**:301 (May) 1941.

Poliomyelitis is a disease which has existed in sporadic form for centuries but which has assumed epidemic proportions in the last fifty years. Its prevalence varies in different countries, but the incidence, even in epidemics, is low when compared with that of the more common communicable diseases. Though its distribution is worldwide, epidemics are usually confined to the temperate regions, and both in epidemic and in endemic form it is a disease of late summer and early fall.

Formerly the incidence of the disease was greater in rural areas, but recent statistical data reveal that the urban and rural populations are affected equally. Poliomyelitis is truly a disease of childhood. The peak of incidence is at the age group of 2 or 3 years. Race incidence has not been adequately studied; however, there is no evidence that any racial immunity exists. It occurs more frequently in males than in females. Persons with blood of group B apparently are

more resistant to the disease than others. The causative agent is a filtrable virus. The portal of entry is subject to considerable controversy, and the mode of transmission is uncertain. The virus has been isolated from stools of infected persons and of apparently healthy contacts. Sewage from infected areas during epidemics has revealed the virus. The incubation period is probably seven to ten days. The period of contagiousness is not definitely fixed. Two theories of immunity exist: subclinical and maturation. Second attacks do occur. Fatality is higher in infants under 1 year, in adults, in males and in urban areas. ORR, Buffalo.

A NOTE ON THE INFLUENCE OF SURGICAL OPERATIONS ON THE DIPHTHERIA ANTITOXIN CONTENT OF BLOOD SERUM. E. SINGER, M. J. Australia **1**:613 (May 17) 1941.

The serum of patients undergoing various operations was tested for antibodies against diphtheria toxin before and within twenty-eight hours after operation. A decrease in titer was noted in one fifth of the cases when the antibody titer was higher than $\frac{1}{20}$ antitoxic unit and in one half of the cases when the titer was lower. These observations suggest that active immunization against noncommunicable diseases, such as wound infections with anaerobes, will probably have its lowest value immediately after wounding. TENNEY, Madison, Wis.

VACCINATION AGAINST EPIDEMIC TYPHUS IN SOUTH AFRICA. M. H. FINLAYSON and G. M. GROBLER, South African M. J. **15**:125 (April 12) 1941.

In guinea pigs three doses of Zinsser-Castaneda vaccine prepared from a Mexican murine typhus strain given at weekly intervals produced a high degree of immunity against South African epidemic typhus which was maintained for at least three hundred fifty-four days. One injection of the vaccine, which had been precipitated by alum, produced a high degree of immunity. This high degree of immunity was not appreciably increased by two injections, at a nine day interval, of smaller doses of the alum-precipitated vaccine. GONCE, Madison, Wis.

SULPHAPYRIDINE, M & B 693, AS A PROPHYLACTIC AGAINST CEREBROSPINAL MENINGITIS. F. C. GRAY and J. GEAR, South African M. J. **15**:139 (April 12) 1941.

During an outbreak of cerebrospinal meningitis in a military camp in Natal, a carrier rate of 22.8 per cent was reduced to 0 per cent by the administration of 1 Gm. of sulfapyridine three times a day for two consecutive days.

GONCE, Madison, Wis.

"PRIMARY" PERITONITIS AS A COMPLICATION OF SCARLET FEVER. M. SIEVERS, Kinderärztl. Praxis **12**:106 (April) 1941.

A case of "primary" peritonitis in a 6 year old girl is described. Five or six days after the onset of scarlet fever, while the rash was still present although it was fading, peritonitis developed. Hemolytic streptococci were found in the exudate but not in the blood. Postmortem examination revealed diffuse, fibrinopurulent peritonitis. This complication is rare. The author states that only 23 cases have been described since 1888. Peritonitis can occur in the early, as well as in the later, stages of scarlet fever. HEYMANN, Cleveland.

THE BORDET-GENGOU MEDIUM IN THE CULTURE OF CEREBRO-SPINAL FLUID AND OF SEROUS EFFUSIONS. J. H. RAYNAL and J. FOURNIER, Chinese M. J. **59**:441 (May) 1941.

The writers believe that an ideal medium for cerebrospinal fluid culture would be polyvalent, permitting growth of various organisms, such as pneumococci, meningococci, Pfeiffer's bacillus and hemophyllic bacteria, and even slow growth of the tubercle bacillus. They report the use of the Bordet-Gengou medium, which has

been so effective in the culture of Bacillus pertussis. They found it useful as a culture medium for tuberculous meningitis as well as for the other organisms just mentioned and report various series of cases of its use. They believe that it permits immediate isolation of even the most exacting micro-organisms found in cerebrospinal fluid, and in many tuberculous infections colonies of the bacilli appear within two or three weeks.

NEFF, Kansas City, Mo.

Acute Infectious Diseases

ACCIDENTALLY TRANSMITTED MALARIA: REPORT OF CASE. MEYER B. MARKS, Arch. Pediat. **58**:357 (June) 1941.

A case of malaria in a 2 month old child is reported. The child had received three intramuscular injections of whole blood, one from the father and two from a laboratory technician.

There was no history of malaria in the 2 donors.

ORR, Buffalo.

SPECIFIC CHEMOTHERAPY OF GIARDIA INFECTIONS. JAMES T. CULBERTSON, J. Lab. & Clin. Med. **26**:1465 (June) 1941.

Atabrine in a dose of 0.1 Gm. twice a day for five days (adult dose) is an effective treatment against the Giardia parasites. It is also effective in these infections in mice and albino rats in the laboratory. Acriflavine was also used in the animals and caused the Giardia parasites to disappear from the albino rats. This drug was not as well tolerated by the animals as atabrine, however.

GARD, Galveston, Texas.

VIRUS DISEASES: SOME LABORATORY PHASES. FRED D. STIMPERT, J. Pediat. **18**:429 (April) 1941.

Stimpert reviews some of the recent advances made in the laboratory studies of virus diseases. He discusses the nature and properties of viruses; their classification, isolation and identification; their cultivation and the serology and immunologic reactions to them, especially the neutralization tests.

RAUH, Cincinnati.

THE PATHOLOGY OF VIRUS DISEASES. ERNEST W. GOODPASTURE, J. Pediat. **18**:440 (April) 1941.

In the study of lesions caused by viruses the interest is focused on the alterations of the cells themselves. Viruses affect cells, often only a restricted type of cell and in ways highly characteristic. Whereas the lesions caused by the commoner bacteria may be of interest primarily in their histologic aspects, those caused by viruses are problems specifically of the participant cells. In verruca vulgaris the virus causes a hyperplasia of epithelial cells. Likewise in molluscum contagiosum the virus affects only the cutaneous epithelium. In other virus infections, such as mumps and poliomyelitis, the specific lesion is a cellular disintegration occurring without hyperplasia or formation of inclusions. In herpes simplex, herpes zoster and varicella inclusions appear in the nuclei of affected cells; in smallpox and vaccinia cellular hyperplasia and lysis are concomitant changes. Another group of virus diseases affects the central nervous system; namely, rabies, poliomyelitis and equine encephalomyelitis. In rabies the virus brings about destruction of nerve cells and causes the deposition in neuronal cytoplasm of characteristic structures, the Negri bodies, specific cellular inclusions. The virus of equine encephalomyelitis, in contrast to those of rabies and poliomyelitis, appears in the blood stream and attacks interstitial tissue as well as neurones. Goodpasture concludes this article with a discussion of the pathogenesis of rabies and poliomyelitis, including recent experimental work.

RAUH, Cincinnati.

ACUTE APPENDICITIS AND PSEUDOAPPENDICITIS IN RHEUMATIC CHILDREN. ALFRED G. LANGMANN, J. Pediat. **18**:599 (May) 1941.

An attack of rheumatic fever in children may begin with or be accompanied by abdominal pain which may exhibit features closely simulating those of acute appendicitis. The differentiation of acute appendicitis from pseudoappendicitis in rheumatic children may be extremely difficult. Pseudoappendicitis occurs almost invariably at the onset of a rheumatic attack, and the abdominal pains may be the first manifestation to appear. These pains may be diffuse in the beginning but they frequently localize in the right lower quadrant. The pains diminish and tend to disappear in the course of two to six days, and as this occurs pains in the joints may appear. The abdominal pain and the articular pain may set in at the same time, suggesting the diagnosis of rheumatic fever. Symptoms and signs indicative of acute appendicitis occurring later in the course of an attack of rheumatic fever are more likely to be due to acute appendicitis than to pseudoappendicitis of rheumatic origin. The erythrocyte sedimentation rate is a useful diagnostic aid. In acute appendicitis, unless perforation has occurred, the rate is normal, whereas in pseudoappendicitis of rheumatic origin the rate is high. The case histories of 19 rheumatic children admitted to the hospital with the tentative diagnosis of acute appendicitis have been reviewed. Ten were subjected to laparotomy; acute appendicitis was found in 4. Langmann stresses the point that if after a brief period of observation there is a reasonable doubt as to the existence of acute appendicitis laparotomy should be done. If the condition is found to be rheumatic, no great harm will be done by operation.

RAUH, Cincinnati.

THE VALUE OF CONVALESCENT CARE FOR RHEUMATIC CHILDREN. LEO M. TARAN, J. Pediat. **18**:737 (June) 1941.

One hundred and ten rheumatic children 6 to 14 years of age were observed at the St. Francis Sanatorium for Cardiac Children. This group was compared with a control group of 110 children from the Kings County Children's Cardiac Clinic. The period of observation was the same for both groups (thirty-six months). The treated group gained three times as much weight as the control group in the same period of time. The incidence of infection of the upper respiratory tract in the treated group was one-fourth that in the control group for the same period of time. Rheumatic recurrence was infrequent at the sanatorium and one half as common in the treated group after convalescent care as in the control group. No sequential relation between infections of the upper respiratory tract and rheumatic recurrences was observed. The incidence of rheumatic recurrences after convalescent treatment is four times as high in children who return to a "poor" home environment as in those who have "good" living conditions at home.

RAUH, Cincinnati [AUTHOR'S SUMMARY].

Chronic Infectious Diseases

SYPHILIS IN BROTHERS: TRANSFUSION SYPHILIS; THE OCCURRENCE OF POSITIVE SPINAL FLUIDS AFTER A PREVIOUSLY NEGATIVE EXAMINATION; THERAPEUTIC FAILURE OF TWO USUALLY EFFECTIVE TREATMENTS FOR SYPHILIS. CLARENCE S. LIVINGOOD and HERMAN BEERMAN, Am. J. Syph., Gonor. & Ven. Dis. **25**:67 (Jan.) 1941.

Two patients are presented in whom syphilis derived accidentally from the same strain of organisms through blood transfusion passed through a relatively similar course in spite of the use of different systems of antisyphilitic treatment. Both had abnormal spinal fluid after they had received a usually adequate amount of antisyphilitic therapy and normal spinal fluid after the treatment. These patients serve to illustrate the dangers of the use of a donor whose syphilitic status is not determined and the exceptions to the usually good prognostic import of a negative result of examination of the spinal fluid in a case of early or late syphilis. If

either patient had been observed alone, one might have the impression that the drug used was responsible for the apparent failure, but the simultaneous observations of the two patients revealed the possible host and strain factors in the case and reemphasized the need for controls in the clinical testing of antisyphilitic drugs.

ROYSTER, University, Va. [AUTHORS' SUMMARY].

REINFECTION IN CONGENITAL SYPHILIS. RICHARD D. HAHN, Am. J. Syph., Gonor. & Ven. Dis. **25**:200 (March) 1941.

In this article the author reviews the literature on reported cases of congenital syphilis in which there was supposed to be reinfection. However, he states that up to the present there have been no indisputable second infections in patients with congenital syphilitis. In the article are reported 2 cases of adequately treated congenital syphilis in which reinfection occurred. These cases appeared to conform rather closely to the rigid criteria for both the congenital and the acquired infection. In the first case there was a clinical and serologic negativity for thirteen years. In the second case, although the serologic reaction for syphilis at no time became entirely negative, there was at least eight years of clinical negativity, including a normal cerebrospinal fluid, between the congenital and the acquired infection.

ROYSTER, University, Va.

THE PREVENTORIUM AND REINFECTION TYPE TUBERCULOSIS. ELI FRIEDMAN and BERNICE W. BILLINGS, Am. Rev. Tuberc. **43**:383 (March) 1941.

The value of the preventorium care of children with first infection type tuberculosis has been questioned by some observers. As a contribution to the solution of this problem, Friedman and Billings studied the subsequent histories of 914 children discharged from their institution since 1922. They divided them into two groups, one of which had been under observation for ten years or more and one for less than ten years. In the first group, tuberculosis subsequently developed in 9, of whom 2 died; in the second group, the disease developed in 3. In a comparable group of 446 untreated children, observed for an average of eleven and three-tenths years, reported by observers who have questioned the value of such care, tuberculosis had developed in 45 and 22 were dead of this disease. Theoretically it would seem evident that removal from contact and proper hygienic care would go far toward stabilizing a primary infection in children and preventing the development of active tuberculosis later. From the authors' experience it would also appear that the optimum age for building up resistance is from 6 to 12 years.

EUGENE SMITH, Ogden, Utah.

POSTRHAGADIC SCARS. ERNEST A. STRAKOSCH and LAWRENCE M. NELSON, Arch. Dermat. & Syph. **43**:664 (April) 1941.

The authors report the following conclusions:

1. Postrhagadic scars of congenital syphilis are distinguished by diminution in the color of the lip, by partial loss of the mucocutaneous border and by the presence of linear furrows of the lip which extend into radial scarlike lesions of the surrounding skin.

2. The lesions, although they appear scarlike, are in reality atrophy of the elastic tissue and not true scars; they belong in the group of secondary atrophic conditions of the skin.

JACKSON, Iowa City.

A COMPARISON OF THE RESPONSE OF YAWS AND SYPHILIS IN THE RABBIT TO THERAPY WITH MAPHARSEN AND NEOARSPHENAMINE. B. J. LONGLEY, N. M. CLAUSEN and A. L. TATUM, J. Pharmacol. & Exper. Therap. **71**:49 (Jan.) 1941.

The authors state that clinical yaws is said to be as difficult of cure as syphilis but that experimental proof of this is lacking. They therefore treated rabbits

with testicular syphilis and yaws with single doses of mapharsen and neoarsphenamine, and after a suitable period extracts of their testicles were injected into testicles of other rabbits. Failure of evidence of syphilis or yaws to develop in the latter animals was considered as proof of the efficacy of the treatment. The data show that there is no essential difference in the ease with which the two diseases may be cured.

PILCHER, Cleveland.

NATURALLY OCCURRING TUBERCULOSIS IN DOGS AND SOME OTHER ANIMALS. R. LOVELL and E. G. WHITE, Brit. J. Tuberc. **35**:28 (Jan.) 1941.

Concluding a previous communication dealing with tuberculosis in dogs, the authors report their findings in a small series of other animals. The disease was found in 4 of 110 cats examined. The primary lesion was discovered most frequently in the alimentary tract. These animals seem highly resistant to the human type of tuberculosis. Bovine bacilli were the organisms most frequently found in all reported cases. Among sheep, while in most cases reported the condition has been due to the bovine type, recently several reports of infection by the avian type have been published, especially in the United States of America. The same preponderance of the bovine type of infection seems to prevail in goats. Mink and silver fox held in captivity suffer from bovine tuberculosis, probably as a result of their being fed raw meat from infected animals. In the horse the primary infection is usually in the alimentary tract, followed by generalization. The infecting organism is usually the bovine type of bacillus, although a few cases have been recorded in which it was the avian type.

EUGENE H. SMITH, Ogden, Utah.

FREQUENCY OF ALLERGY TO TUBERCULOSIS IN THE CHILD. J. P. GARRAHAN and P. R. BAGNATI, Arch. argent. de pediat. **12**:79 (Feb.) 1941.

The authors are able to show that a pronounced decrease in tuberculous infection has taken place in the children of Buenos Aires, Argentina, and that there has been also a pronounced decrease in the morbidity from tuberculosis.

SCHLUTZ, Chicago.

VACCINATION OF CHILDREN BY THE CALMETTE AND GUERIN METHOD IN THE MUNICIPALITY OF CORDOBA. G. SAYAGO and I. NAPUT, Arch. argent. de pediat. **15**:120 (Feb.) 1941.

The general mortality of children vaccinated with BCG is less than that of those not so vaccinated. Death occurs in 15.6 per cent of those not vaccinated and in 8.3 per cent of those vaccinated. The greater part of the mortality of those vaccinated was found in the first trimester of life, in contrast to the mortality of the nonvaccinated group, which was higher toward the end of the first year.

SCHLUTZ, Chicago.

BIRTH WEIGHT AND GAIN OF THE TUBERCULOUS CHILD. C. A. URQUIJO and M. WAISSMANN, Arch. argent. de pediat. **15**:234 (March) 1941.

Advanced maternal tuberculosis is often the cause of prematurity in the infant. The birth weight of the infant born of a mother with moderate tuberculosis is not different from that of the healthy nontuberculous infant born of a healthy mother. Prematurity of an infant born of a mother with advanced tuberculosis is due not directly to the tuberculous infection of the mother but to her general low state of health. The gain in weight of a tuberculous infant born with a normal weight is similar to that of the infant born of a healthy mother. The gain in weight of the infant weighing less than 2,500 Gm. born of a tuberculous mother is similar to that of the infant of equivalent weight born of a nontuberculous mother.

SCHLUTZ, Chicago.

FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS IN INFANTILE TUBERCULOSIS. A. SELLEK AZZI and A. DEL FRADE, Arch. de med. inf. **10**:61 (Jan.-March) 1941.

The authors studied 100 cases and came to the conclusion that in childhood tuberculosis one will encounter an occasional positive serologic reaction for syphilis, although it was definitely shown that patients with this type of reaction were free from syphilis. Why these false positive reactions occur is so far not explained.

SCHLUTZ, Chicago.

INDEX OF TUBERCULINIZATION IN ARGENTINA. ALEJANDRO A. RAIMONDI and JULIO PALACIO, Rev. méd. latino-am. **26**:365 (Jan.) 1941.

This is a survey of the incidence of tuberculosis infection, as determined by the tuberculin test, in various regions of Argentina. Some of the studies were made as far back as in 1906, and therefore no worthwhile comparisons can be made with present conditions. Recent tests among medical students show that from 71.7 to 90.6 per cent give positive reactions. In all regions the incidence in children under 6 years of age is 44.5 per cent. In the frequency of first infection type of tuberculosis, infants and children as a group are being replaced by young adults.

DWYER, Kansas City, Mo.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE PRESENT STATUS OF THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS. ARTHUR C. DEGRAFF, Bull. New York Acad. Med. **17**:423 (June) 1941.

The author reviews the various methods of treatment of subacute bacterial endocarditis and states that none of the methods now employed is effective. A ray of hope is seen in sulfanilamide and its derivatives as possible agents for the future treatment of this condition. Recent reports in this field are not yet fully convincing.

JAHR, Omaha.

THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS. S. S. LICHTMAN and WILLIAM BIERMAN, J. A. M. A. **116**:286 (Jan. 25) 1941.

The recent use of chemotherapy in treating subacute bacterial endocarditis has produced a few recoveries reported in the literature. Previously only isolated instances of spontaneous recovery were reported. Along with sulfanilamide and its derivatives the authors have combined the use of heparin and of fever therapy by vaccine and by artificial fever. In a series of 200 cases there was a 6 per cent recovery rate after the use of sulfanilamide and its derivatives. Of 43 patients treated with chemotherapy and heparin, 11.5 per cent recovered. Four of 24 patients with physically induced hyperthermia and 5 of 21 treated with vaccine-induced hyperthermia and chemotherapy recovered. Combined therapy seems to be most favorable.

HEERSMA, Kalamazoo, Mich.

CHANGES IN THE CHEMICAL COMPOSITION OF THE BLOOD COMING FROM DAMAGED TISSUES. HANS SELYE and CHRISTINE DOSNE, Proc. Soc. Exper. Biol. & Med. **47**:143 (May) 1941.

Confirming other work, the authors found that shock did not develop until the tourniquet which occluded the blood vessels in 6 Macaca mulatta monkeys was released. In that edema did not develop until after symptoms of shock had set in, the phenomenon could not be explained by the loss of fluid in the damaged area. Subsequent experiments with rats, rabbits and cats, and also with adrenalectomized mice suggested that shock may be caused by "the lack of something rather than the excess of a toxic metabolite." Injection of blood from an anoxic extremity of a rabbit into adrenalectomized mice, which are particularly susceptible to toxic substances, with no untoward effects tends to disprove the toxic theory of shock. Experiments with rats and cats reveal that there is a loss of sugar from the

blood of the damaged extremity, whereas the nonprotein nitrogen and hemoglobin are increased. From these facts it is suggested that shock may be due to lack of certain vital substances in other parts of the body because of the excess utilization of these substances by the metabolism in the involved area and therefore not the result of injurious compounds from the damaged tissue. Although this is but a working hypothesis for the theory of shock, it fits the experimental facts better than any other theory.

HANSEN, Minneapolis.

ACUTE THROMBOPHLEBITIS OF UNKNOWN ETIOLOGY. A. C. FISHER, South African M. J. **15**:131 (April 12) 1941.

The author describes 21 cases of an acute febrile illness accompanied by thrombophlebitis of one or more veins occurring among young adults living in the copper-mining area of northern Rhodesia.

GONCE, Madison, Wis.

DO YOU KNOW THAT? ALBERTO ROBLES, Prensa med. mex. **6**:45 (April 15) 1941.

The sudden attacks of infantile acetonemia may at times lead to diagnostic errors; the subcomatose child gives off a strong odor of acetone. This is found when the urine is examined.

The first impression is that one is dealing with diabetic coma. But the satisfactory general condition compels one to reject the idea of diabetes; the somnolence is rarely coma and rapidly disappears, and the blood sugar is normal.

Occasionally the urines have sugar, although it is observed that this glycosuria is unstable and indicates a transient crisis of hepatic insufficiency like acetonemia.

The author states that he has never seen acetonemia lead to diabetes, at least in children.

GIFFEN, Toledo, Ohio.

TECHNIC RECOMMENDED FOR BLOOD TRANSFUSIONS IN BABIES. E. G. CASELLI, Rev. Soc. de pediat. de La Plata **2**:18 (April-May) 1941.

The general technic to be followed for transfusions, including proper selection of a donor, blood grouping, use of anticoagulants and the method and speed advisable in giving the blood, and the possible accidents are briefly discussed. In the author's practice the giving of transfusions to babies with bronchopneumonia has been accompanied by a fall in the death rate from 58 to 28 per cent.

HIGGINS, Boston.

ARTICULAR MANIFESTATIONS IN LEUKEMIA. T. HALBERTSMA, Kinderärztl. Praxis **12**:105 (April) 1941.

Halbertsma describes a case of chronic leukemia in a girl 10 years of age who had pains in different joints accompanied by fever. The clinical similarity of the articular manifestations to those observed in patients with rheumatic fever was striking. No response was obtained to salicylates, however. Postmortem examination confirmed the diagnosis of leukemia.

HEYMANN, Cleveland.

Diseases of Lungs, Pleura and Mediastinum

BRONCHIECTASIS. JOHN CHAPMAN and HENRY HOSKINS, Am. Rev. Tuberc. **43**:512 (April) 1941.

In a study of the relations between varieties of bronchiectasis and the signs and symptoms associated with them 116 cases were analyzed (60 cases of the cylindric, 26 of the saccular, 24 of the varicose, 4 of the fusiform and 2 of the bronchiolectatic type). The last two forms were disregarded because of their limited numbers. The distribution according to age did not show any marked differences between the various types. Spitting of blood occurred more frequently in the cases of the saccular type. About 50 per cent of all patients denied having had pneumonia, but its incidence in the history of patients suffering from the saccular

type of disease was significantly greater than in the history of those with the cylindric.

A history of influenza (73 per cent) and of nasal disease (35 per cent) was obtained, distributed about equally among the three principal varieties. Physical signs were lacking more often in the presence of cylindric bronchiectasis than in the other varieties, as were also significant incidents in the histories as obtained from these patients. The location of the disease in this series was found to be relatively more frequent in the lower lobe of the right lung than in the left lung.

The authors admit that these studies are relative rather than absolute and acknowledge that histories are notoriously unreliable. It seemed advisable to divide their cases arbitrarily into the three groups used, due to the polymorphism of bronchiectasis. Where one or more types of dilatation were found, they have used the predominant type in their classification, tending always to consider the saccular type as the diagnosis when it was present along with varicose or cylindric forms, and the varicose as the definitive type if present in conjunction with cylindric dilatations.

EUGENE SMITH, Ogden, Utah.

CLASSIFICATION OF CHRONIC BRONCHIECTASIS. JOHN CHAPMAN and DAVID MCCULLOUGH, Am. Rev. Tuberc. **43**:521 (April) 1941.

Not only should a practical working classification of bronchiectasis be based on morphologic varieties, but account should be taken of the relation of clinical and etiologic factors to the pathologic changes. The authors suggest the following (abbreviated) classifications:

I. The etiologic factor
   - A. Congenital bronchiectasis
   - B. Primary bronchiectasis
   - C. Acquired or secondary bronchiectasis

II. The anatomic factor
   - A. As to morphology of dilatation
   - B. As to location
   - C. As to degree of dilatation
   - D. As to associated pathologic changes

III. The Functional factor
   - A. Symptomless
   - B. Dry, hemoptysic
   - C. Mild productive
   - D. Severe
   - E. Septic

IV. The prognostic factor
   - A. Progressive
   - B. Nonprogressive
   - C. As to health and life.

EUGENE SMITH, Ogden, Utah.

CHYLOTHORAX: REPORT OF A CASE IN AN INFANT. MICHAEL A. BRESCIA, Arch. Pediat. **58**:345 (June) 1941.

A case of spontaneous chylothorax in a 13 month old boy is presented. The patient recovered by repeated thoracentesis and expectant treatment. The anatomy, embryology, histology and physiology of the thoracic duct is reviewed.

Serial roentgenograms illustrating the progress of the case are submitted.

ORR, Buffalo.

PNEUMONIA IN INFANCY AND CHILDHOOD. W. J. AUGER, ALAN BROWN and W. J. ANGER, Canad. M. A. J. **44**:496 (May) 1941

Sulfapyridine has reduced the case fatality rate in patients under 2 years of age with pneumonia caused by various bacteria from 20 per cent in those treated nonspecifically to 5.6 per cent in those receiving the drug.

Sulfapyridine has shortened the course of pneumococcic pneumonia in patients between 2 and 14 years of age.

MOORE, Omaha.

STUDIES OF THE EXPECTORANT ACTION OF IODIDES. LOUIS TUFT and NATHANIEL M. LEVIN, J. Allergy **12**:416 (May) 1941.

Bronchial secretions were obtained with a bronchoscope at five minute intervals following intravenous injections of sodium iodide and oral administration of potassium iodide. In some instances salivary secretions and specimens of urine were obtained.

The iodide appeared in the bronchial secretions in fifteen to twenty-five minutes after intravenous injection, and in a slightly longer time after oral administration. The iodides were given on an empty stomach.

Urinary excretion was distinctly delayed.

The work was done on 6 patients.

HOVER, Cincinnati.

SEVERE INTESTINAL HEMORRHAGE COMPLICATING LOBAR PNEUMONIA: A CASE OF DIEULAFOY'S EROSION IN A 5 YEAR OLD CHILD. HARRY H. CLEMENS, J. Pediat. **18**:524 (April) 1941.

Dieulafoy's erosion (gastritis ulcerosa, ulcerative gastritis and hemorrhagic ulcerative gastroenteritis) is a rare and often fatal complication of pneumonia. Five cases of this complication, up to this report, have been described in the American literature. Two patients were adults, and 3 were children; of these, 2 children have survived. This condition is characterized by the formation of gastric or gastrointestinal ulcers or erosions in the course of pneumonia (usually lobar pneumonia, but occasionally bronchopneumonia). No satisfactory reason for the development of the ulcerations has ever been advanced. A case of lobar pneumonia accompanied by enterorrhagia (Dieulafoy's erosion) in a 5 year old girl is reported; the child recovered after the use of sulfapyridine and transfusions.

RAUH, Cincinnati [AUTHOR'S SUMMARY].

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

STAPHYLOCOCCIC ACTINOPHYTOTIC (BOTRYOMYCOTIC) ABSCESS OF THE LIVER WITH PULMONARY INVOLVEMENT. A. A. FINK, Arch. Path. **31**:103 (Jan.) 1941.

The term "staphylococcic actinophytosis" refers to a granulomatous lesion resulting from infection with Staphylococcus aureus. This disease ran a chronic and fatal course over a period of one year in a white boy of 16 years. His history began with furunculosis and a subcutaneous abscess with constitutional symptoms. Pneumonia, bronchiectasis, purpura, secondary anemia, nephritis, icterus and abscess of the liver were diagnosed during the course. Staph. aureus was isolated from the cutaneous lesions, liver and blood.

Necropsy revealed an enlarged liver (3,400 Gm.) containing an abscess connected to the right lung by a sinus. The abscess was a multiloculated cavity, 12 cm. in diameter, with a thick fibrous wall and a shaggy lining. Similar smaller cavities surrounded it. The right pleural space was obliterated by fibrous adhesions. No nodules were seen in the substance of the right lung. Two small nodules were observed in the lower lobe of the left lung. The kidneys were large and swollen.

Coalescing tuberculoid lesions of varying sizes were seen on microscopic examination of the liver. These lesions had walls of thick collagenous and loose fibrous tissue with central areas of liquefaction containing acute inflammatory cells and coccoid micro-organisms. The nodules in the left lung had a similar

histologic picture. Acute and subacute glomerulonephritis was present in the kidneys.

The author presents the ninth case of actinophytosis in human beings to be reported in the literature.

SHERMAN, Chicago.

GENERAL ABDOMINAL LYMPHADENOPATHY. ABRAHAM O. WILENSKY, Arch. Surg. **42**:71 (Jan.) 1941.

The author prefaces his comprehensive discussion of this subject by stating that it has come to be fairly recognized that there exists in children and young adolescents an acute abdominal condition of moderate or severe grade, which is similar in its general manifestations to appendicitis, diverticulitis, etc., but in which the predominant discoverable observations at operation consist of only an inflammatory enlargement of the mesenteric and retroperitoneal lymph glands in the ileocecal angle. This condition usually develops in patients between 3 and 18 years of age. It is during this period of life that the lymphatic apparatus of the human being is under continual and variegated stress and is most apt to undergo pathologic changes. It is pointed out that strains of streptococci are usually the cause of the lymphadenopathy.

General abdominal lymphadenopathies are similar to lymphadenopathies in other regional areas. In the abdomen many of them are parts of a distinct symptom complex, such as typhoid fever or dysentery. Others are related to loosely gathered clinical entities known collectively as the "rheumatic" group of diseases. A large group seems to be related to a preceding "catarrhal" or "throat" infection, and this seems to have some relation to forms of glandular fever, or infectious mononucleosis, and what is clinically known as abdominal grip.

Treatment must follow along the lines known by experience to be correct and adequate for the original disease. Conservative treatment is indicated if one can perfectly diagnose the condition so that the fear of undiscovered acute appendicitis or other surgical emergency can be definitely eliminated. This can usually not be assured, so an exploratory abdominal operation is the treatment advised.

KAISER, Rochester, N. Y.

THE ABSORPTION OF VITAMIN A IN CELIAC DISEASE: INTERPRETATIONS OF THE VITAMIN A ABSORPTION TEST. CHARLES D. MAY and JOHN F. MCCREARY, J. Pediat. **18**:200 (Feb.) 1941.

Studies of the vitamin A absorption test in a group of patients with celiac disease and related conditions are reported. The test was performed as follows: A dose of 0.1 cc. of percomorph liver oil per pound of body weight was given by mouth. Blood levels of vitamin A before the oil was given and three, five, seven, nine and twelve hours afterward were determined. Results showed that in normal infants and children the level of vitamin A in the blood rises 52 to 231 U. S. P. units from three to five hours after the administration of the oil, the average rise being 130 U. S. P. units. In celiac disease the average rise was 8.2 U. S. P. units. Infants and children presenting the clinical features of the celiac syndrome secondary to the effect of an underlying disorder, such as fibroses of the pancreas, malnutrition and chronic otitis media, showed a similar low rise in vitamin A blood levels following the test. The vitamin A absorption appears to return to normal during recovery from celiac disease. The test is not a specific diagnostic test for celiac disease and is of limited value in differentiating celiac disease from other conditions producing the celiac syndrome. The level of carotenoids in the blood in celiac disease seems to follow the clinical course of the disease, being low during the active stage and rising with clinical improvement.

RAUH, Cincinnati.

CONGENITAL MEGACOLON: REPORT OF A CASE TREATED BY SYMPATHECTOMY. F. E. KREDEL and M. W. BEACH, J. South Carolina M. A. **37**:11 (Jan.) 1941.

The signs and symptoms of congenital megacolon are commonly called Hirschsprung's disease. It is briefly described in a case report of a Negro boy 3½ years

of age who had excellent results after a sympathectomy. Considerable enlargement of the abdomen persisted. The main object of the operation is to overcome the constipation; removing the fibers allows peristalsis.

WESTON, Columbia, S. C.

ANOREXIA OF PERPLEXING ORIGIN. JESSE R. GERSTLEY, M. Clin. North America **25**:147 (Jan.) 1941.

A boy of 11 years commenced to show abnormal drowsiness about four months previous to admission to the hospital, and polydipsia, polyuria and marked anorexia subsequently developed, and later vomiting. He continued to be mentally alert in spite of the drowsiness. By intensive clinical and laboratory studies, encephalitis, diabetes insipidus and endocrine dysfunction were ruled out as responsible for his condition. The anorexia became intensified, and finally it was necessary to resort to tube feeding. By this means it was possible to give him a high caloric diet, which he retained, although all attempts at feeding by mouth resulted in vomiting. He continued to show good intelligence and had all the physical manifestations of profound depression with no evidence that he actually felt depressed.

At this juncture, when diagnostic progress seemed definitely halted, a more intensive study of the history was made. It was found that the symptoms had been slowly progressive over a period of a year instead of four months and were characterized by diabetes insipidus (which seemed to have corrected itself), mental change, anorexia and now vomiting. This history together with loss of weight in spite of sufficient calories suggested malignancy, with the location probably cerebral. This tentative diagnosis was confirmed by the subsequent development of changes in the superficial reflexes, failure of the pupils to react to light, increasing drowsiness and finally the finding of xanthochromic spinal fluid and the demonstration of a cerebral neoplasm. At autopsy a firm ovoid tumor was found replacing the base of the third ventricle, compressing the posterior portion of the optic chiasm and the anterior border of the pons. The sylvian aqueduct was occluded and pushed to the left, and the tumor had almost completely destroyed the corpus callosum. No vestige of the pineal body was found in the pineal recess. Histologically the lesion proved to be a teratoma of the pineal body. In conclusion Gerstley emphasizes the value of painstaking, frequently repeated history taking as the mainstay of good clinical pediatrics.

EUGENE SMITH, Ogden, Utah.

EUMYDRIN [ATROPINE METHYLNITRATE] IN THE TREATMENT OF HYPERTROPHIC PYLORIC STENOSIS: AN ANALYSIS OF 40 CONSECUTIVE CASES. HELEN M. M. MACKAY, Arch. Dis. Childhood **16**:1 (March) 1941.

Forty consecutive patients with hypertrophic pyloric stenosis have been treated with atropine methylnitrate (eumydrin), with a mortality of 12.5 per cent; 31 of them were cured by the drug and 4 more by operation. Of the 5 deaths, 4 were due wholly or in part to enteritis contracted in the hospital, and 1 was probably due to excessive administration of fluid. Thirty-five babies showed disappearance of, or reduction in, obstruction at the pylorus after treatment with atropine methylnitrate. Of the 5 who showed no response, all had a high fluid intake, which was probably the factor which prevented the drug's bringing about relaxation of the pyloric spasm. Excessive fluid intake was accompanied by a less rapid response to atropine methylnitrate, a slower gain in weight and often a poor appetite. There was no evidence of benefit from routine gastric lavage. Diagnosis was based on the following points: (*a*) a history of copious projectile vomiting associated with constipation; (*b*) visible gastric peristalsis; (*c*) a palpable pyloric tumor, which varied in consistency under the examiner's hand (sometimes repeated examinations were necessary to elucidate this), and (*d*) in 34 cases in which roentgen ray examination was carried out, delay in emptying the stomach. The delay, as usual, varied. In the majority it was marked, but in some clinically typical cases it was slight. The maximum dose of atropine methylnitrate given to a baby has

varied from 2 to 7 cc. of a 1:10,000 aqueous solution, given before each of six, or occasionally seven, feedings in the twenty-four hours, or 1.2 to 4.2 mg. of the drug in the day.

KELLY, Milwaukee.

Nervous Diseases

ASTROCYTOSIS ARACHNOIDEAE CEREBELLI: A RARE MANIFESTATION OF VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS. A. EARL WALKER, Arch. Neurol. & Psychiat. **45**:520 (March) 1941.

A 16 year old girl who had signs of cerebellar dysfunction and evidence of hypopituitarism for many years and a pronounced hydrocephalus died suddenly after a ventriculographic examination. Postmortem examination revealed a neurofibroma of the abdominal and thoracic sympathetic centers and astrocytosis of the meninges over the right cerebellar hemisphere. The glial overgrowth extended into the fourth ventricle, obstructing the foramens of Luschka and Magendie.

BEVERLY, Chicago.

TREATMENT OF SYDENHAM'S CHOREA WITH NIRVANOL [PHENYLETHYLHYDANTOIN]. HARRY M. GREENWALD and BERNARD GREENBERG, Arch. Pediat. **58**:48 (Jan.) 1941.

Twenty-one of 22 patients with chorea were successfully treated with nirvanol (phenylethylhydantoin), with no untoward effects. The average period of hospitalization after the onset of treatment was twenty days. The method of treatment, blood picture and clinical course in each case are described. A uniform dose of 2½ grains (0.16 Gm.) three times daily was given until a reaction occurred. A leukopenia was observed in 18 cases, with a return to normal after administration of the drug was discontinued; in no case was any bad effect discernible from the leukopenia. In 20 cases an eosinophilia, with the eosinophil count ranging from 2 to 18 per cent, was noted. Leukopenia and eosinophilia alone are not a reliable index for the interruption of treatment.

ORR, Buffalo.

EPILEPSY: ITS TREATMENT WITH A PHENOBARBITAL-BELLADONNA SYNERGISM. CLEMENT E. SCHOTLAND and LEWIS H. LOESER, Arch. Pediat. **58**:87 (Feb.) 1941.

Twelve children suffering from epileptic phenomena were studied. Eleven had grand mal seizures. One had pyknolepsy. They were treated with varying doses of phenobarbital and the total levorotatory alkaloids of belladonna in tablet form. There was a marked reduction in the number and severity of the seizures in 9 of them while under treatment. In 2 patients, including one with pyknolepsy, there was no improvement. One patient was classified as having a probable spontaneous remission.

ORR, Buffalo.

INSTITUTIONAL EPILEPSY IN RELATION TO CHILD NEUROLOGY. SAMUEL M. WEINGROW, THOMAS S. P. FITCH and ALBERT W. PIGGOTT, Arch. Pediat. **58**:142 (March) 1941.

Eight hundred cases of institutional epilepsy have been studied with regard to etiology, aura, neurologic disturbances, seizure frequency and encephalographic findings.

The authors emphasize that the etiologic diagnosis is made in many instances by a careful study of the past personal history. In 450 cases a relation between possible causative agents and onset of convulsions was found. The average age of onset was 11.2 years, indicating, according to the authors, a greater need for a more thorough neurologic study of childhood convulsions.

Auras were noted in 243 cases and when present had in most cases definite localizing value.

ORR, Buffalo.

CEREBRAL SPASTIC PARALYSIS: THE OBSTETRIC HISTORY OF 185 CASES. GERALD W. GUSTAFSON and GEORGE J. GARCEAU, J. A. M. A. **116**:374 (Feb. 1) 1941.

The birth histories of 185 patients with cerebral spastic paralysis were reviewed. Premature delivery and use of injections of posterior pituitary were frequent. Evidence of asphyxia was absent in the majority. Anesthesia and analgesia seemed to play little part in this series, most of the deliveries being made at home, with labor of less than twelve hours' duration. The proper management of labor constitutes the best prevention of cerebral spastic paralysis.

HEERSMA, Kalamazoo, Mich.

TOXOPLASMIC ENCEPHALITIS IN CHILDREN. ALBERT B. SABIN, J. A. M. A. **116**:801 (March 1) 1941.

Two cases are presented of this disease, which in only 1 previous instance was proved to have occurred in a human being. In 1 of these cases death occurred. Injection into mice of macerated brain from this case produced a disease recognized as caused by the parasite Toxoplasma.

Symptoms included convulsions, disorientation, fever and pleocytosis. There was no such sign of meningeal irritation as nuchal rigidity, and the spinal fluid was sterile. Inoculations in mice showed a late change except when the brains were reinoculated, which produced a more rapidly fatal disease. Neutralizing antibodies were present in the patients' blood, which may offer a more rapid method of testing.

HEERSMA, Kalamazoo, Mich.

FURTHER STUDY OF CENTRAL STIMULATION FROM SYMPATHOMIMETIC AMINES. J. W. SCHULTE, E. C. REIF, J. A. BACHER JR., W. S. LAWRENCE and M. L. TAINTER, J. Pharmacol. & Exper. Therap. **71**:62 (Jan.) 1941.

It was previously noted that while deeply narcotized animals are not aroused by some of the amine compounds, after they are aroused they show actions resembling stimulation of the higher brain centers, such as "gnawing at the wire [of cages], licking their tails, rubbing their noses, and so on." The present paper presents results of a study of effects of seventy-five amines on white rats to learn whether the amines at present used as central stimulants could be shown to be active experimentally and whether others would be as effective or better. In brief, it was found that dextroamphetamine was the most active of the entire group. Various isomers of the ephedrine group had some central stimulating power but much less than the dextrobenzedrine. Levoepinephrine produced effective cerebral stimulation only in doses that could not be tolerated by the circulatory system. No central stimulation was produced by such clinically effective compounds as tyramine synephrin and neo-synephrin.

PILCHER, Cleveland.

DANGERS OF RADIATION WITHOUT BIOPSY OF BRAIN TUMORS IN CHILDREN. FRANC D. INGRAHAM and JAMES B. CAMPBELL, New England J. Med. **224**:925 (May 29) 1941.

This case report is presented in the hope that disastrous results similar to those described may be avoided. The patient had a good prognosis in other respects, and the total and permanent blindness that developed was due, the authors believe, to the fact that irradiation was performed for over two years in another hospital in the mistaken belief that the tumor of the brain was a medulloblastoma. Subsequent operation by the authors proved it to be a fibrillary astrocytoma.

There is a general impression that medulloblastoma, which every one agrees is radiosensitive and an almost hopeless surgical lesion, is the most common intracranial tumor of childhood. In the authors' series of 104 cases of verified tumors, there have been 21 children with medulloblastomas and 39 with astrocytomas. The patients were all under 15 years of age. For the age group in question, the figures are very similar to those in Bailey, Buchanan and Bucy's series (30 astrocytomas, 13 medulloblastomas) and in Cushing's series (40 astrocytomas, 24 medulloblastomas).

In view of these several considerations, the authors consider a biopsy essential for an accurate diagnosis. GENGENBACH, Denver.

ARSENIC AS A POSSIBLE CAUSE OF SUBACUTE ENCEPHALOMYELITIS. ARTHUR D. ECKER, New York State J. Med. **41**:335 (Jan. 15) 1941.

Subacute, fatal encephalomyelitis has symptoms similar to arsenic poisoning. These symptoms are headache and fatigue, both bodily and intellectual. A picture resembling neurasthenia, dizziness and other cerebral symptoms may be present. It is practically impossible to remove patients from all contact with arsenic. The central nervous system, bones and hair contain more arsenic than the gastro-intestinal canal and liver. In this study complete microscopic and chemical observations were made, and the presence of 0.1 mg. of arsenic per hundred grams of tissue was considered significant. All cases of syphilis were removed from the series, and any chance of confusion from embalming fluids or formaldehyde solution used in preserving the tissues was eliminated.

The patients were mostly adults, but a child of 4 months, who died with a diagnosis of malnutrition and cerebral edema, was found to have 0.3 mg. of arsenic per hundred grams in the brain tissue. A girl 14 years of age, with a diagnosis of epilepsy, athetosis and mental deficiency had 0.83 mg. After thorough study Ecker was convinced that 12 cases of subacute encephalomyelitis were really instances of chronic arsenical poisoning. AIKMAN, Rochester, N. Y.

Psychology and Psychiatry

THE CHILD-PARENT RELATIONSHIP: THE CHILD IN THE FAMILY. CLIFFORD SWEET, LAWRENCE R. JACOBUS and HENRY E. STAFFORD, J. A. M. A. **116**:38 (Jan. 4) 1941.

Discussing the common problems encountered by parents, such as crying, refusal to eat, excess activity, etc., the authors speak of the importance of regularity, reasonableness and discipline in avoiding these problems. Satisfactory parent-child relations, which are as important in the family as physical health, depend to a great extent on following the principles suggested in this article.

HEERSMA, Kalamazoo, Mich.

CLINICAL STUDY OF MONGOLIAN IDIOTS IN THE PROVINCE OF SASSARI, WITH PARTICULAR REFERENCE TO LESIONS OF THE OCULAR FUNDUS. A. MASIA, Riv. di clin. pediat. **39**:65 (Feb.) 1941.

Case reports on 22 mongolian idiots were given. There was no relation between consanguinity in the ancestors and the appearance of mongolism. Among the parents of these children 4 had alcoholism and 9 malaria. The youngest mother was 22, 8 were between 35 and 40 and 12 were over 40. Several of the mothers had had abortions in the pregnancy preceding the birth of the child with mongolism. However, in all cases in which Wassermann tests were made (16 mothers and 16 children) there were negative reactions. Only 3 of the children had cardiac murmurs. Of the 22 infants seen in the clinic since 1928, 9 have already died.

A characteristic picture in the eyegrounds of the afflicted children was a marked ring of pigmentation around the optic disk. The pigment gradually faded toward the periphery of the retina, presenting in places a picture suggesting the retina of the albino. This change was also present at the macula, suggesting in many respects the findings in amaurotic family idiocy (Tay-Sachs disease). One child showed a pepper and salt distribution of the retinal pigment.

HIGGINS, Boston.

JUVENILE DELINQUENCY. A. FAVRE and E. GENET, Ztschr. f. Kinderpsychiat. **7**:146 (Jan.) 1941.

This is a discussion of the various phases of juvenile delinquency. Particular stress is laid on the problems of the incorrigible child and the conflicts of the

adolescent. The legal and moral views are discussed, and statistics from various European institutions analyzed. The medical-social angles of the problems of delinquency are reviewed. Cases are submitted which illustrate the different implications.

JAHR, Omaha.

THE STUDY OF JUVENILE CRIMINALS IN THE ZURICH CANTON. J. LUTZ, Ztschr. f. Kinderpsychiat. **7**:162 (Jan.) 1941.

This article records a ten year study of juvenile criminals in the canton of Zurich, Switzerland. The object of the investigation was to ascertain the reactions of the children to certain phases of life and its effect on the progress of their criminality.

JAHR, Omaha.

THE FUNCTIONAL SIGNIFICANCE OF CERTAIN ALTERATIONS IN LANGUAGE. VICTOR FONTES, Ztschr. f. Kinderpsychiat. **7**:173 (March) 1941.

The functional significance of organic nerve lesions are discussed and illustrated by a case report.

JAHR, Omaha.

PSYCHIATRIC OBSERVATIONS ON CHILDREN DURING THE WAR IN FINLAND, 1939-1940: GENERAL IMPRESSIONS. J. BRANDER, Ztschr. f. Kinderpsychiat. **7**:177 (March) 1941.

This paper deals with impressions gained during the bombardment of Helsinki during the Russo-Finish War. The author states that psychic reactions among children varied from mild to very severe. The most bewildering problems developed during the period beginning with voluntary or obligatory evacuation of the children. In this group reactions ranged from anorexia to parvus nocturna. During each actual bombardment the reactions were severe from the beginning of the alarm until the abatement of the raid. Whereas the adults, as a rule, became accustomed to the fray as bombardments became frequent, with the children terror increased with every succeeding alarm. The author feels certain that the psychologic effects of the war on the children will be productive of permanent damage to the psychic state.

JAHR, Omaha.

THE MISTREATED CHILD. J. E. STAEHELIN, Ztschr. f. Kinderpsychiat. **7**:187 (March) 1941.

This is a dramatic case report which does not lend itself to abstracting.

JAHR, Omaha.

Diseases of the Genitourinary Tract

THE SIGNIFICANCE OF URINARY p_H: CRITICAL OBSERVATIONS. MILTON A. BRIDGES and MARJORIE R. MATTICE, Ann. Int. Med. **14**:1123 (Jan.) 1941.

The authors not only review the literature regarding p_H of the urine but also report their own observations. They consider the normal range of p_H to fall between 4.6 and 8.0. Also considered is the urinary p_H of patients with alkalosis, acidosis and other pathologic conditions and of patients who have been given drugs.

GARD, Galveston, Texas.

MALIGNANT RENAL NEOPLASMS IN CHILDREN. C. C. HIGGINS and F. L. SHIVELY JR., Arch. Surg. **42**:386 (Feb.) 1941.

The most common malignant growth affecting the kidneys of infants and children is the Wilms tumor. It is estimated that tumors of the kidney comprise approximately 25 per cent of all malignant tumors occurring in childhood. It was pointed out that there is still considerable confusion as to the exact origin of this neoplasm. It is thought that the tumors originate from the renal blastema.

In a review of 26 cases it was noted that progressive enlargement of the abdomen is the first apparent abnormality. This was noted in 60 per cent of

this series and was present at the time of examination in 25 of the 26 children. Pain, hematuria, nausea, vomiting, loss of weight and shortness of breath occur later as the mass enlarges. With the present facilities for investigation of the kidneys, establishment of an accurate diagnosis is usually not difficult.

As a Wilms tumor is radiosensitive and diminishes markedly in size during the course of roentgen therapy, this procedure is recommended before operation. Nephrectomy is the operation of choice. Postoperative roentgen therapy is also advised. The prognosis in the series studied was grave. At the end of five years one half of the patients had died and no accurate follow-up report was available for the remaining cases.

KAISER, Rochester, N. Y.

ATTEMPTS TO PRODUCE URINARY CONCRETIONS IN THE MONKEY WITH PROMIN. JOHN A. TOOMEY and WILLIAM S. TAKACS, J. Pediat. **18**:10 (Jan.) 1941.

Large doses of promin (a sodium salt of p,p'-diaminodiphenyl-sulfone-N,N'-di-[dextrose sulfonate]) were given intramuscularly to 14 Macaca mulatta monkeys. Ten monkeys were killed at the end of ten days, and 4 were allowed to live a few days longer to note if any cumulative side effects would occur. Even with massive doses used, five or more times as much as the largest dose recommended for human beings, there was no evidence in the kidneys of the formation of stones or crystals. Some of these monkeys had an increase in blood urea, and the question is raised as to whether or not an increase in the blood nitrogen levels may occur first, with the crystals formed secondarily or at least concomitantly.

RAUH, Cincinnati.

THE EFFECT OF ATROPINE, PILOCARPINE, PROSTIGMINE, ESERINE, MECHOLYL AND EPHEDRINE ON THE TONUS AND CONTRACTION MECHANISMS OF THE URINARY BLADDER, WITH OBSERVATIONS ON THE CLINICAL APPLICATION OF THESE DRUGS. HARRY A. TEITELBAUM and ORTHELLO R. LANGWORTHY, J. Pharmacol. & Exper. Therap. **72**:152 (June) 1941.

The authors experimented with anesthetized cats. All drugs used, except atropine, had a strong stimulating effect on both the tonus and the contractility of the bladder. A striking confirmation of the experimental work was the use of pilocarpine in treatment of 2 patients suffering from paralysis of the bladder with retention and overflow. After a few days of the subcutaneous use of pilocarpine hydrochloride in each case, bladder control resulted, and 1 subject was able to tell when he was going to urinate fifteen to thirty seconds before the flow started; the second subject could not tell when urination was to start or when it was finished. This beneficial effect continued without further use of the drug.

Atropine has a selective inhibitory effect on the bladder. It can lower a high state of tone and abolish rhythmic activity, whether these states are present normally or are due to stimulating activity of a drug. Atropine can strongly inhibit bladder contractions due to action of a drug, but it can only slightly inhibit bladder contractions that are normally present.

PILCHER, Cleveland.

CLINICAL OBSERVATIONS ON TESTICULAR TUMORS IN CHILDREN. M. TAWARA, Acta pediat. japon. **47**:322 (March) 1941.

Tawara reports his clinical observations on 4 cases of adenocarcinoma and 1 case of teratoma of the testis in children. In the latter case, the tumor originated from the intra-abdominal testis in a 3 month old infant and histologically consisted of epidermis with hair, sweat and sebaceous glands and bone, cartilage and fat tissues, as well as of smooth muscle and sympathetic ganglion cells. Testicular adenocarcinoma was seen in 4 instances in children between the ages of 1 year and 7 months and 4 years and 3 months, in each one occurring in the left testis. The growth of the tumors was very rapid, and the children, 3 with surgical removal and 1 without, had metastatic formations in various organs; all of them died after a period of from eight to twenty-two months. Roentgen therapy of high voltage which was instituted in 1 case apparently produced no clinical improvement.

KATO, Chicago.

Diseases of the Ductless Glands; Endocrinology

CLINICAL EXPERIMENTS WITH MIXTURES OF STANDARD AND PROTAMINE ZINC INSULINS. HELMUTH ULRICH, Ann. Int. Med. **14**:1166 (Jan.) 1941.

With clinical experiments, the author attempts to show that these two insulins mixed in a syringe are suitable for clinical use. He feels that the results are as predictable as when one uses standard and protamine zinc insulins in separate injections. A mixture of 3 parts of standard insulin and 2 parts of protamine zinc insulin appeared to give the most promising results.

GARD, Galveston, Texas.

CONGENITAL HÜRTHLE CELL TUMOR. DOUGLAS SYMMERS, Arch. Path. **31**:99 (Jan.) 1941.

The author presents a case of Hürthle cell tumor in a 6 week old female infant. She had a progressive swelling in the region of the thyroid gland, present since birth. Respiratory distress necessitated an emergency operation. A portion of the growth extended through the upper aperture of the thorax and was not surgically accessible. An estimated four fifths (47 Gm.) of the growth was removed. The patient continued to show signs of respiratory embarrassment after operation. She was discharged improved.

The ultimate cell derivation, thyroid, parathyroid or otherwise, was not apparent on microscopic examination. The histologic picture was that of an adenoma, but the possibility of malignancy was not denied, because the description was based on tissue removed surgically. Illustrations accompany this report.

SHERMAN, Chicago.

HYPERTHYROIDISM IN CHILDREN. CHARLES GILMORE KERLEY, Arch. Pediat. **58**:92 (Feb.) 1941.

The author's report covers 104 patients. Twenty-nine were males and 75 females. The ages at the first consultation were as follows:

2½ to 5 years	8	(3 male, 5 female)
5 to 10 years	58	(17 male, 41 female)
10 to 16 years	38	(9 male, 29 female)

Medical management consisted of the use of iodized salt in cooking and compound solution of iodine U. S. P. in small doses; further lines of treatment are governed by the age of the patient, physical findings and the nature and degree of the nervous instability. Cessation of school activities is essential. Often a change of environment and human contacts will be of real benefit. Surgical measures were found necessary in the majority of instances in spite of what was considered adequate medical care

ORR, Buffalo.

SUPPRESSION OF LACTATION BY TESTOSTERONE. PAUL V. DUFFY and JOSEPH CORSARO, J. A. M. A. **116**:33 (Jan. 4) 1941.

Administration of 50 to 75 mg. of testosterone propionate over a period of two to three days beginning the second day after delivery prevents lactation in 18 of 25 cases. Given earlier or after lactation was started, it had little effect. Small doses were used to relieve engorgement and pain in the breasts while lactation was maintained.

HEERSMA, Kalamazoo, Mich.

OBESITY IN CHILDHOOD AND ENDOCRINE TREATMENT. HILDE BRUCH, J. Pediat. **18**:36 (Jan.) 1941.

The case is reported of a 6 year old boy who became very obese while receiving gonadotropic substance. Another case is reported of an 11 year old girl who grew obese after an enlargement of the thyroid had been noted. It could be demonstrated in both instances that the obesity stood in causal connection with the diagnosis and treatment respectively. These stimulated or aggra-

vated an overanxious and protective attitude of the families, which led to overfeeding and restriction of activity and thus to obesity. Bruch continues this paper with a discussion of thyroid and pituitary preparations in the treatment of obesity, the relation of obesity to cryptorchidism and the dangers of endocrine therapy in childhood. Bruch concludes that the diagnosis of an endocrine disorder in an obese child and long-continued glandular treatment are not only unjustified but harmful, so far as they produce or increase the apprehensive and oversolicitous attitude of the parents and block the road for a rational treatment of the obesity.

RAUH, Cincinnati.

THE TREATMENT OF GRAVES' DISEASE [EXOPHTHALMIC GOITER] IN CHILDREN. NORMAN NIXON, J. Pediat. **18**:71 (Jan.) 1941.

Nine cases of exophthalmic goiter in children are reported. One child could not be followed. Two patients were treated conservatively, and, while their symptoms were mild, both made complete recoveries. The remaining 6 patients were treated surgically, with 4 deaths registered within one year following surgical intervention. Two died within two days following thyroidectomy; another death occurred three months later during anesthesia administered prior to tonsillectomy; the fourth child died in diabetic coma one year after the subtotal thyroidectomy. The other 2 patients treated surgically have shown some improvement, but insufficient time has elapsed since the operation to judge the results. At autopsy, observations consistent with those characteristic of status thymicolymphaticus were made on 3 of the 4 children who died. Nixon concludes the report with the observation that it would seem advisable to treat exophthalmic goiter in children on a conservative basis because the thyroid is probably not the primary pathogenic factor and the changes in the thyroid are but one manifestation of the general picture. In addition the thyroid plays a tremendously important part in the growth and development of the child. Thyroidectomy should be performed only for those children who do not show definite improvement after a comparatively long period of treatment on a carefully planned and executed medical regimen.

RAUH, Cincinnati.

HYPOTHYROIDISM IN INFANTS AND CHILDREN. ROBERT P. GOODKIND and HAROLD L. HIGGINS, New England J. Med. **224**:722 (April 24) 1941.

Although cretinism has for many years been known to result from deficiency of thyroid secretion, and although thyroid has had wide use in its treatment, an exact basis for a clear statement of the fate of treated cretins is still wanting. Observations have been made on 23 patients (13 from the Harriet Lane Home and 10 from the Children's Metabolism Clinic of the Massachusetts General Hospital) who had been under sustained treatment for thyroid deficiency (cretinism) for five and a half to twenty-four years.

The diagnosis was made before the patient was 1 year old in 9 cases, and under 2 years in another case. Analysis of these histories indicates congenital thyroid deficiency (cretinism). Experience at the Children's Metabolism Clinic of the Massachusetts General Hospital has indicated that the daily dose of thyroid U. S. P. necessary to maintain normal metabolic function in completely athyreotic children is ¼ grain (0.015 Gm.) per year of life up to 6 years of age; 1½ grains (0.09 Gm.) is sufficient for older children and adults.

It has been the practice at the Massachusetts General Hospital to photograph each untreated cretin; this is a valuable procedure, since the signs and symptoms of cretinism disappear within a few weeks after treatment with thyroid is begun; a later review of the case for diagnosis is thus made more satisfactory.

Six patients were found to have intelligence quotients between 90 and 112; 6, between 70 and 89, and 10, below 70. Although the mean intelligence quotient was higher in the patients of normal physical growth than in the dwarfed, 2 of the dwarfed group had normal intelligence, and many of normal size were mentally retarded. The age of diagnosis and beginning of treatment was usually less for the ultimately mentally retarded patients than in those of normal intelligence.

The criterion that 1½ grains of thyroid U. S. P. daily will raise to normal the basal metabolism of the athyreotic patient over 6 years of age is confirmed. The degree of thyroid deficiency, as measured by the amount of thyroid necessary to maintain normal metabolism, is not proportional to the degree of mental retardation. The cholesterol content in blood serum or plasma shows close correlation with the basal metabolic rate.

Determinations of the basal metabolic rate and the blood cholesterol level following the withdrawal of thyroid therapy are of diagnostic significance in the doubtful cases of treated cretinism. GENGENBACH, Denver.

RELATION BETWEEN THE ENDOCRINE GLANDS AND PHOSPHATASE OF THE BLOOD SERUM AND OF THE BONE. B. CERA, Riv. di clin. pediat. **39**:97 (Feb.) 1941.

The amount of phosphatase in 100 cc. of serum or 100 Gm. of bone (diaphysis of the femur) is expressed in the number of milligrams of inorganic phosphorus liberated in forty-eight hours at 37 C. from a 2.5 per cent solution of sodium betaglycerophosphate.

The phosphatase of the blood serum and of the bone of normal guinea pigs was 82 and 302 mg., respectively; in thyroidectomized guinea pigs the figures were 72 and 270 mg.; in guinea pigs given diiodotyrosine they were 68 and 245 mg., while guinea pigs treated with thyroxin showed 90 and 325 mg. It would thus appear that phosphatase was increased by thyroxin and diminished by thyroid sedatives and thyroidectomy.

The phosphatase in normal rabbits amounted to 64 mg. in the serum and 271 mg. in the bone; in thymectomized rabbits, 84 mg. in the serum and 302 mg. in the bone, and in guinea pigs given endothymine, 75 and 266 mg. Thus, the thymus seems to decrease phosphatase action. HIGGINS, Boston.

CORRELATION OF FRIEDREICH'S ATAXIA AND DIABETES MELLITUS. G. KOHNE, Deutsche med. Wchnschr. **67**:177 (Feb. 14) 1941.

In 1935 Curtius, Storring and Schonberg described the cases of 2 sisters who suffered from Friedreich's ataxia and diabetes mellitus. Eighty per cent of the living blood relatives were examined without finding any evidence of either of the two diseases. The authors postulated disturbance of the metabolism of carbohydrates due to a lesion of the central nervous system.

Five years later the sisters died of diabetic coma at the ages of 26 and 28 years. A complete autopsy performed in each case showed typical changes characteristic of Friedreich's ataxia. The hypophyses and the midbrains were found to be normal in both cases. However, the pancreas of each woman showed severe primary atrophy of the islands of Langerhans. Therefore, the two diseases could not be interpreted on the common basis of an abnormality of the central nervous system. KERESZTURI, New York.

Diseases of the Muscles, Bones, Joints and Lymph Glands

RELIABILITY AND SIGNIFICANCE OF THE GORDON TEST IN HODGKIN'S DISEASE. PAUL E. STEINER, Arch. Path. **31**:1 (Jan.) 1941.

In 1932 Gordon described a syndrome in rabbits and guinea pigs receiving intracerebral injections of a broth suspension of lymphogranulomatous tissue. It consisted of spastic paralysis, incoordination and ataxia, retraction of the head, fits and loss of weight. The author presents a study of the reliability and significance of the test.

In 21 cases of histologically proved Hodgkin's disease the reaction was positive in 16 and negative in 5. No positive results were obtained in 40 control tissues, including lymphosarcoma, pseudoleukemia, leukemia, nonspecific lymphadenitis and tuberculous lymphadenitis. Of 310 cases previously reported in the literature, in 73.9 per cent the reaction was positive, whereas in 452 control cases collected from the literature there was a positive reaction in 1.77 per cent. Most positive reactions in controls were observed in lesions easily differentiated microscopically.

The anatomic basis for the symptom complex produced in animals lies in degenerative changes in the Purkinje cells of the cerebellum. The agent producing this reaction has been found in human leukocytes, leukocytic cream from eosinophilic blood, myelocytic leukemia blood cream, normal human bone marrow, normal human spleen and other normal and pathologic tissues, as well as in the lymph nodes of patients with Hodgkin's disease. Its properties are those of a nonliving agent. The Gordon reaction is nonspecific, but it is reliable in differential diagnosis of lymph node diseases if it is accompanied by histologic examination.

SHERMAN, Chicago.

HODGKIN'S DISEASE IN CHILDREN. D. J. M. MCCAUSLAND, Arch. Dis. Childhood **16**:59 (March) 1941.

Of the 13 patients with Hodgkin's disease admitted to the Hospital for Sick Children, Toronto, Canada, in the past ten years, 11 have been boys. The youngest was 4 years old, the oldest 12 and the average age 8 years. The average duration of symptoms before death was nineteen months, the shortest three months and the longest four and a half years. Eleven of these children had enlarged cervical glands, and 1 had enlarged axillary glands, on admission. Studies of the blood showed no characteristic changes but a varying degree of secondary anemia and decrease in lymphocytes. Diagnosis depends on biopsy. Treatment consists in roentgen ray therapy, the aim being to obtain as long remissions as possible.

KELLY, Milwaukee.

DYSTROPHIA MYOTONICA IN INFANTS AND CHILDREN. OTTO MAAS, Brit. J. Child. Dis. **38**:59 (April-June) 1941.

Dystrophia myotonica (myotonia atrophica) is an endogenous, hereditary disease of the nervous system that usually affects many persons of different generations in the same family. It not infrequently manifests itself during childhood. The principal symptoms are wasting of muscles and weakness associated with myotonia. Baldness, early cataract and other symptoms resulting from disturbed endocrine glands and mental abnormalities are also observed in many persons affected by this disease.

In families in which the father or mother suffered from this disease many of the children showed physical and mental abnormalities more or less suggestive of dystrophia myotonica. They either were mentally backward or had an abnormality of temperament, i. e., persistent and almost morbid cheerfulness, mild grandiosity and a lack of drive and initiative.

Since a cure for the disease has not yet been discovered, early diagnosis leading to special guidance is essential.

LANGMANN, New York.

Surgery and Orthopedics

TRAUMATIC SHOCK AND SYMPATHETIC OVER-STIMULATION. J. W. TOMB, South African M. J. **15**:109 (March 22) 1941.

The author discusses Freeman's hypothesis that the collapse of the circulation in surgical and traumatic shock is the result of overstimulation of the sympathetic nervous system and his demonstration that shock can probably be successfully treated in its early stages by paralysis of the sympathetic nervous system by the use of ergotoxine. He also observes that this probability "receives support from the recent successful employment of ergotoxine . . . as an antidote to the lethal effects of scorpion toxin, part of which is a strong stimulant of the sympathetic nervous system (Hassan and Mohammed, 1940)."

GONCE, Madison, Wis.

PREOPERATIVE AND POSTOPERATIVE CARE OF CHILDREN. C. ABAD MARTINEZ, Prensa méd. mex. **6**:37 (March 15) 1941.

Once surgical intervention is decided on, every effort should be made to reduce the risk before the operation. A complete history is obtained, and complete

clinical examination is made and chemical examination of the blood. If during the preliminary examination a complicating factor is found, the rule is to correct it before operation, unless it is an emergency operation. If the stomach, bladder and intestines are empty, there is less difficulty with the anesthesia, and the postoperative course will be better.

It is very important that the surgeon and his assistants gain the confidence of children whose nervous systems are the seat of the most active reactions and support very poorly the loss of nervous energy, thus giving rise to grave disturbances. The preoperative psychic reaction in children depends largely on the anesthetic employed. Generally a barbiturate is used as a sedative before the anesthetic is given. This not only exercises a beneficial mental sedation but may cause the child to sink into crepuscular sleep, facilitating the narcosis and diminishing the amount necessary for its continuance. During the postoperative days an intelligent nurse is of inestimable value and it is not useless to repeat that the technical perfection with which an operation has been executed gives no guarantee of the later course when this matter is neglected. At the completion of the operation the physician and the nurse should accompany the child back to its room and remain there until complete return of consciousness; steps should be taken to relieve pain.

GIFFEN, Toledo, Ohio.

Miscellaneous

TWINS T AND C FROM INFANCY TO ADOLESCENCE: A BIOGENETIC STUDY OF INDIVIDUAL DIFFERENCES BY THE METHOD OF COTWIN CONTROL. ARNOLD GESELL and HELEN THOMPSON, Genet. Psychol. Monogr. **24**:13 (April) 1941.

This extensively documented monograph is the report of a longitudinal study of a pair of monozygotic twins from early infancy to adolescence. The similarities and disparities of the twins were intensively studied in order to assess the relative importance of nature and nurture in determining these similarities and differences and also to assess the stability of resemblances and differences.

The data presented include longitudinal measurements of physical status, motor behavior, adaptive behavior, language behavior and social behavior. Objective analyses were also made of cinematographic records.

The authors conclude that the disparities and similarities are due to genetic factors and are uninfluenced by environment. The twins were not much more alike in infancy than in adolescence. One of the twins was subjected to hundreds of hours of specialized training designed to improve her motor coordination, neatness, constructiveness, span of attention and vocabulary. None of these added to her mentality, personality or ability. In general the similarities and disparities between the twins remained the same from infancy to adolescence.

WEINFELD, Highland Park, Ill.

A NEW PEDIATRIC FORMULARY USING "FUNCTIONAL WEIGHT." DAVID PILLAR, Rev. méd. munic. **1**:524 (April) 1941.

The doses are based on kilograms of the child's weight for twenty-four hours. Functional weight is the evaluation in kilograms of all factors that can influence dosage. Many pages are devoted to the formulary and should be read by those interested. In solutions 1 cc. corresponds to 1 Kg. for twenty-four hours; in powder for oral use, 0.10 Gm., and for rectal use, 10 cc.

SANFORD, Chicago.

ACUTE CARBON MONOXIDE POISONING. J. J. CRICCO and L. A. MAGISTOCCHI, Rev. Soc. de pediat. de La Plata **2**:72 (April-May) 1941.

A review of the symptoms and treatment of carbon monoxide poisoning is followed by a short description of 2 cases in which the patient recovered.

HIGGINS, Boston.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

EDWARD A. PARKS, M.D., *President*

HUGH MCCULLOCH, M.D., *Secretary*

Fifty-Fourth Annual Meeting, Skytop, Pa., April 30–May 2, 1942

(Concluded from page 201)

Fourth Session

Friday Evening, May 1

Some Physiologic Aspects of Acidosis. DR. HAROLD L. HIGGINS, Boston.

Chemical, physiologic and clinical data indicate a definite cerebral control over the acid-base equilibrium of the blood. The acidosis of relative anoxemia (second wind, high altitudes, pneumonia) is cerebral in type. The acidosis associated with encephalitis, toxemia, cerebral trauma and diabetes has a definite cerebral component. Caffeine, a cerebral stimulant, leads to acidosis, which in premature infants may prove fatal. Morphine, a depressant, tends to cause alkalosis.

An analogy may be drawn between the heat center of the brain for controlling the body temperature and an acid-base center for controlling the reaction of the blood. In both instances one finds diurnal variations and effects from physiologic, pharmacologic and pathologic factors. The acid-base center will call on means of production, of elimination or of neutralization of acid or alkali in amounts needed to reach a newly determined level and in ways depending on conditions present in the body. Dehydration or hydration of the blood is one way of effecting a change in the reaction of the blood toward the acid or alkaline side.

Acetone bodies are produced in the body in the absence of carbohydrate catabolism when there is a call to bring the blood to a more acid level. The formation of acetone bodies is highest in the alkalosis of severe vomiting. It is not the quantitative factor in diabetic acidosis, as the degree of acidosis is not proportional to the amount of acetone bodies in the blood and urine; in fact, a person with diabetes may go into severe acidosis and coma without any acetonuria. Attacks of severe acidosis and coma in patients with diabetes may occasionally depend on diseased kidneys associated with cloudy swelling but usually are cerebral in origin, being initiated by such factors as hyperglycemia, sudden change of dietary or other habits, fatigue or emotional stress.

DISCUSSION

DR. JAMES L. GAMBLE, Brookline, Mass.: I find Dr. Higgins' concept of an acid-base center in the brain to govern the reaction of body fluids rather startling. It is an entertaining suggestion and will give much to think about. I am not sufficiently fluent in metaphysical chemistry to appraise it without reflection. I do, however, entirely agree with Dr. Higgins' main thesis: that many, indeed most, of the changes found in a physicochemical system in the body should be regarded not as defects but as adjustments; that is, they should be recognized as changes which are necessary for the survival of the system in the presence of obstacles imposed by disease.

Hence there is clearly before physicians the problem of how to tell a defect from an adjustment, and this opens the gate to a delightful region of debate

and discussion. The bars are down. The premise of teleology is permitted. I am a devout teleologist, in spite of the many gibes I have received from Dr. Darrow. But I doubt whether I should have had the temerity to suggest that ketosis is an adjustment and not a pathologic event. Dr. Higgins has this kind of bravery, and I admire him for it.

DR. HAROLD L. HIGGINS, Boston: I might say that in this report I have talked for fifteen minutes and have not used the term hydrogen ion concentration or p_H. Acidosis may still be presented in the terms of acid and alkali.

Relation of Vitamin C to Scarlet Fever, Rheumatic Infections and Diphtheria in Children. DR. ARTHUR F. ABT, DR. L. MARTIN HARDY (by invitation), DR. CHESTER J. FARMER (by invitation) and DR. JESSIE D. MAASKE (by invitation), Chicago.

This paper will be published in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Treatment of Type-Specific Haemophilus Influenzae Infections During Infancy and Childhood. DR. HATTIE E. ALEXANDER (by invitation), MISS CATHERINE ELLIS (by invitation) and MISS GRACE LEIDY (by invitation), New York.

Evidence was presented for the conclusion that a combination of sulfanilamide or one of its derivatives and type-specific rabbit serum is the treatment of choice for all severe Haemophilus influenzae infections in children. The severe infections fall into three categories: meningitis, pneumonia accompanied by empyema and bacteremia in infants under 1 year, and obstructive infections of the respiratory tract of the type often termed laryngotracheobronchitis. Our evidence for the effectiveness of these agents is derived from three sources: investigation of the biologic features of H. influenzae, comparison of the protective value in mice of the therapeutic agents singly and combined and the results obtained when these agents are combined in the treatment of meningitis in children.

The results obtained from these sources may be summarized as follows:

Biologic Features of H. Influenzae.—As has been shown to be true for pneumococcic infections, all evidence suggests that in recovery from H. influenzae infections, whether as the result of therapy with sulfanilamide or one of its derivatives, serum therapy or a combination of these, antibody is an essential part of the recovery mechanism.

Comparative Protective Values.—Results of comparison of protective value in mice of sulfanilamide and sulfadiazine and serum singly and combined are summarized in the following table.

Therapeutic Agent	Average Protection	
	No. of M. L. D.	No. of Mice Used
Sulfanilamide	500	120
Sulfadiazine	8,500	145
Serum alone	17,750	490
Serum + sulfadiazine	1,000,000	135

The numbers representing the comparative values are the average protections expressed in minimum lethal doses obtained from a series of tests. The number of mice used in obtaining these figures is listed for each value. They suggest certain conclusions:

A. When sulfanilamide and sulfadiazine are administered in equal quantities, sulfadiazine affords superior protection in mice. However, the concentration of drug in the blood is higher in the mice receiving sulfadiazine. Comparison of the maximal protection by these drugs is complicated by the fact that sulfanilamide in quantities greater than 1.5 Gm. per kilogram in twenty-four hours proves toxic to mice, whereas sulfadiazine is well tolerated in doses of 3 Gm. per kilogram.

B. It has not been possible to demonstrate a significant difference between the average protection afforded by sulfadiazine administered twice daily for three days and serum given intraperitoneally in one dose when each is used alone. Comparison of maximal protection given by these two agents used singly shows a value of 100,000 minimum lethal doses for serum and 10,000 for sulfadiazine.

C. When these two agents are combined, the results are superior to those obtained with either alone.

Results Obtained in Treatment of Meningitis with Combination of Sulfanilamide and Rabbit Serum.—Thus far we have records of 50 patients with H. influenzae meningitis treated with a combination of specific rabbit antiserum and sulfanilamide or one of its derivatives. To 33 of the 50 patients antibody was administered both intrathecally and intravenously; to 17, by the intravenous route only. On the basis of our experience in this group, the latter mode not only is justified but is considered the treatment of choice for all patients. Intrathecally injected serum has seemed to be of additional value only in patients in whom the infection has assumed a chronic form.

The age incidence of patients treated and results of therapy in the different age groups are presented in the following table.

Age Distribution of Patients with H. Influenzae Meningitis Who Recovered and Who Died

Age	Total Number	Recovered	Died	Per Cent Recovered
3 - 7 months	8	2	6	25
7 -12 months	3	3	0	100
1 - 2 years	14	13	1	92
2 - 3 years	18	13	5*	72
3 - 4 years	1	1	0	100
4 - 5 years	5	5	0	100
Over 5 years	1	0	1	0
Total	50	37	13	
Percentage of recovery of patients over 7 months of age				83

* In 2 cases, leukopenia; in 2 cases, insufficient treatment.

DISCUSSION

DR. JAMES D. TRASK, New Haven, Conn.: Dr. Alexander has introduced this treatment of influenza in New Haven, and I can corroborate all of the things she has said. It seems interesting that there has been a great increase in this disease in New Haven and probably in a good many other cities.

I might say that since 1927 my associates and I have taken cultures of the heart's blood in all fatal cases in our service and have seen that every case of meningitis was well studied bacteriologically. I think my impression is correct when I say we averaged about 2 cases a year from 1927 to 1939. Since then we have had somewhere between 10 and 15 examples a year of severe infection with Haemophilus influenzae, and most of them have been meningitis. Also we have had about 4 or 5 cases yearly of these rapidly progressing laryngitides, and they are apt to be unbelievably severe. The whole course of the disease may be only twelve hours. They are described by Sinclair and Fousek.

They are characterized by laryngitis with high fever and signs of shock, and there are large numbers of influenza bacilli in the blood cultures. These generally grow in a matter of ten or twelve hours. I cannot say anything about the treatment of other types of conditions, such as pericarditis, peritonitis and laryngitis, in which Dr. Alexander's serum has been used, but I can say that our results

with her method in cases of meningitis have been excellent. I think we have lost 3 patients out of about 16 or 18, and those 3 were children under 6 months. I did not expect to be here and hence my figures may be inaccurate by 1 case, but I am very close to telling the truth.

DR. JOHN A. V. DAVIES, Boston: Dr. Alexander's excellent results are a tribute to her intelligent study of this serious disease and as well to her painstaking attention to details, all or some of which may at times be important in weighing the balance in favor of the patient. As is generally known, in the past one of the chief drawbacks of experimental work has been the lack of a suitable susceptible animal, and her studies with mice are a valuable approach to the problem, particularly of the combined use of serum and chemotherapy.

Our results obtained in recent years at the Children's Hospital in Boston with horse serum were so discouraging that we welcomed an opportunity to try out her rabbit serum when she offered it to us in 1940. Our first 2 patients recovered, and when it became difficult at times to get a fresh supply of rabbit serum from New York we made some serum in our own laboratory by a somewhat different method.

Our results with horse serum had been very discouraging. Since 1937, 80 per cent or slightly more of the patients had died. To enumerate some of the difficulties in evaluating our successes and failures, one might mention the difference in age and resistance of the patient and variations in the virulence of the organism, in the amount of horse serum given and in the route by which it was given. We gave serum both intravenously and intraspinally in varying amounts. Fresh human serum was also given intraspinally as complement to promote lysis of the organisms. Finally four different sulfonamide compounds were tried.

Therefore, when we started to use rabbit serum, at the very outset we decided to simplify our treatment as much as possible, in order, we hoped, to evaluate our results somewhat more clearly. We decided to use rabbit serum intravenously only. We abandoned entirely intraspinal injections of serum, not only for the purposes of statistical evaluation but because it seemed entirely possible that the inflammatory reaction caused by foreign protein in the subarachnoid space might overweigh any possible benefit from antibodies in this serum.

Contrary to previous teachings, Dr. Eleanor Downs, in our laboratory, found that inflammatory, in contrast to normal, spinal fluid contains significant amounts of hemolytic complement. It seemed unnecessary, therefore, to inject fresh human serum intraspinally.

Our complete results with intravenous rabbit serum I hesitate to offer in comparison with Dr. Alexander's and Dr. Trask's—2 of 7 of the patients treated with Dr. Alexander's serum died, and 3 of 9 treated with our own died, making 5 of 16 who died. Only 2 received no chemotherapy at any time, and these 2 recovered.

These results, on the face of it, appear favorable in comparison with our results with horse serum. As I said, 80 per cent of the patients treated with horse serum in the last five years died. I am quite sure that over a longer period of years our figures would be somewhat better than that; moreover, one must remember that we used horse serum by somewhat more complicated methods. It is entirely possible that, for instance, the intraspinal injection of horse serum in large amounts is in itself deleterious. We also did not take pains when using horse serum, as we now do when using rabbit serum, to establish the fact that we had a positive balance of antibody in the circulating blood.

At the present time I am inclined to agree with Dr. Alexander that rabbit serum is probably the serum of choice as compared with horse serum. It remains to be seen, however, whether or not concentrated horse serum under comparable conditions might produce comparable results.

We are inclined to continue the use of serum by the intravenous route alone and to accept the growing amount of evidence that, although serum remains the

most important agent in specific treatment, sulfadiazine and sulfathiazole, as Dr. Downs showed by in vitro studies some two years ago in our laboratory, probably constitute a valuable adjunct in the treatment of influenzal meningitis.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: In the work of my colleagues and me on the effect of specific serum on pertussis, we have in a way followed the trail blazed by Dr. Alexander in her work on Haemophilus influenzae. It is now interesting to hear her describe the apparent therapeutic effectiveness of sulfadiazine on infections produced by H. influenzae, because we have observed a similar beneficial effect of this drug on the course of experimental murine pertussis.

We have successfully treated 2 of our last 3 patients with H. influenzae meningitis with combinations of serum and a derivative of sulfanilamide, for one using sulfathiazole and for the other sulfadiazine.

Dr. Alexander mentioned the most interesting application of the use of specific rabbit globulin in the treatment of obstructive laryngitis. I should like to ask how many of the patients showed the presence of the specific carbohydrate of H. influenzae in the blood, and whether she uses the serum only in cases in which it is demonstrable.

DR. WILBURT C. DAVISON, Durham, N. C.: I should like to ask Dr. Alexander whether the patients who had influenza meningitis were treated during the first week of the disease. My impression has been that the mortality was very high in those in whom treatment with sulfanilamide or one of its derivatives was not started until the second week.

DR. HATTIE E. ALEXANDER, New York: In answer to Dr. Bradford's question, it is already clear that all patients with Haemophilus influenzae meningitis do not require serum for recovery. Before serum became available for patients in this group some of them recovered promptly after treatment only with sulfanilamide or one of its derivatives. For these reasons I have been interested in attempting to find a method for separating the most severe infections from the rest. The qualitative precipitin test, which is a crude measurement of the concentration of specific polysaccharide in the patient's serum, is recommended for detecting the severe infections which require serum. Over a 1 cm. column of type B diagnostic serum in a small precipitin tube an equal column of the patient's serum is carefully layered by means of a fine capillary pipet. If the reaction is positive, a white ring forms at the interface. When the ring forms within a ten minute period after the test is set up, the concentration of specific carbohydrate is relatively high, and there is reason to believe that this occurs only in severe infections. Serum is used initially only in those patients whose serums show a positive reaction for precipitin within ten minutes. The need for antibody in all other patients with H. influenzae laryngitis may await the patient's response to treatment with sulfanilamide or one of its derivatives. Three patients have been treated according to this standard, which served as a satisfactory guide.

In answer to Dr. Davison's question, if one disregards the group which I showed on the separate slide, the 10 patients who had been treated with sulfanilamide or one of its derivatives for extended periods, for the majority of patients treatment was started within the first week of the disease. On the other hand, most of that group of 10 patients had had the disease for three weeks, and while the drug used inhibited the course sufficiently so that these patients could respond at this period, it was not able to effect complete recovery.

I believe that when these drugs have been used previously, the period after which one can accomplish something with serum is greatly lengthened, provided the drugs have been given over a continuous period throughout the infection until the time serum is administered.

Seven of the 10 patients recovered even after long periods of treatment with sulfanilamide derivatives which were unsuccessful when used alone.

Precipitin and Agglutinin Formation in Streptococcicosis. Dr. Parker Dooley (by invitation) and Dr. Helen V. Karr (by invitation), Chicago.

DISCUSSION

Dr. James D. Trask, New Haven, Conn.: I also think it is pretty hard to work with the streptococcus, and, as a matter of fact, I don't do it any more (laughter). Dr. Boisvert, in Dr. Powers' department, does, and I occasionally see the results of some of his work. One of the results leads me to ask you a question, Dr. Dooley, and that is, "What do you think are the usual characteristics of the first infection with group A streptococcus in children?"

Dr. Powers and I have a good deal of fun teasing each other about what we think is the nature of a first infection. First we thought it was erysipelas of the newborn, but it is not at all uncommon to see a baby of perhaps a few days or weeks of age who seems perfectly well except for a slight serous nasal discharge. Nose and throat swabs show a practically pure culture of hemolytic streptococci, and these cultures remain positive for several days. We have not carried out any serologic studies to find out whether or not these infants respond with antibodies. I am wondering if this is the usual form of first infection. Can you enlighten me on this point?

Dr. Parker Dooley, Chicago: Now, offhand, I can't tell you what the character of their infection was because I haven't looked at the records of their cases for some time. I think a great many people feel that streptococcic infection in newborn and very young infants is very likely to be a larval infection which does not make the baby very sick.

Still's Disease, Chronic Rheumatoid Arthritis and So-Called Disseminated Lupus Erythematosus. Dr. Paul György, Cleveland.

Several diseases of childhood have been described and studied in the past as independent entities until their nosologic identity with diseases occurring in adults has been recognized. The reverse holds equally true. As examples it will suffice to mention (1) "acute rickets" and scurvy, (2) rickets and osteomalacia and (3) celiac disease and sprue. The question is posed whether a similar merger would not be in order with regard to Still's disease, as well as many forms (probably the majority) of so-called rheumatoid arthritis with the subacute and chronic forms of so-called disseminated lupus erythematosus or, as it is better termed, Libman-Sacks disease. 1. Ed. Note.—A classification of arthritis has been approved by the Nomenclature Committee of the American Rheumatism Association. It appears in the "Standard Nomenclature of Disease" and in a "Primer on Arthritis" in *The Journal of the American Medical Association* (**118**:1091 [Aug. 1] 1942).

Still's disease is commonly characterized by chronic arthritis with synovial participation and without appreciable osseous or cartilaginous deformities and by periods of fever, prostration, loss of weight, polylymphadenopathy and splenomegaly. Pericarditis, anemia and leukopenia are frequent findings. In my own observations cutaneous eruptions, fleeting edema, purpura (petechiae, with or without a white center) and diarrhea with or without blood were not rare complications. The disease may even simulate ulcerative colitis. When the manifestations are more or less limited to chronic arthritis, it is often designated rheumatoid arthritis.

In Libman-Sacks disease the more common clinical features which may be observed in various combinations are fever, prostration, loss of weight, weakness, severe articular involvement, changes in the blood (leukopenia, anemia, thrombopenia), nephritis, hemorrhagic diathesis, cutaneous manifestations, evidence of involvement of the serous membrane (pleuritis, pericarditis, ascites), endocarditis, lymphadenopathy, splenomegaly and gastrointestinal complaints. Thus the symp-

tomatology is about the same as in Still's disease. Furthermore, it should be emphasized that in Libman-Sacks disease, just as in Still's disease or in rheumatoid arthritis, the different symptoms may vary greatly in severity and any of them may be lacking in an individual case.

The clinical course and pathologic changes of Libman-Sacks disease including Still's disease are distinctly different from the course and pathologic changes of rheumatic fever and tuberculosis. The causative agent of Libman-Sacks disease is unknown.

During the past year 7 cases of Libman-Sacks disease have been observed, the form ranging from true acute disseminated lupus (beginning with a discoid lesion) to a chronic condition without cutaneous manifestation. Autopsy in 1 case revealed the presence of mild rheumatic changes combined with the specific picture of Libman-Sacks disease. The outstanding clinical features of some of the other cases will be discussed.

DISCUSSION

DR. EMANUEL LIBMAN, New York: In the first place, I want to thank the members for the privilege of addressing them. Secondly, I want to express my appreciation for the opportunity of presenting a general outline of the subject of so-called Libman-Sacks disease, because I realize the necessity of clarifying the subject.

In 1911, at a postmortem examination, I found in the heart a lesion of the endocardium which was so different from all other varieties of endocarditis that had been described that I wrote on the label "peculiar, important." The recognition of this peculiar endocarditis gave rise to the development of the subject of Libman-Sacks disease. Today we know that the disease can occur without any macroscopic endocarditis.

In 1924, Dr. Benjamin Sacks and I put on record the histories of 4 patients in whom this form of endocarditis was present. The clinical picture was similar in all the cases. In 2 of the cases lupus erythematosus was present and in the other 2 completely absent. It was evident that a febrile disease existed which could occur with or without lupus erythematosus. For want of a better name the condition was called atypical verrucous endocarditis, because the extensive endocarditis was the striking feature at necropsy. It was recognized that a proper designation would not be available until the causative factor was discovered.

The lesions of this form of endocarditis are free from bacteria, and Aschoff bodies and other stigmas of rheumatic fever are absent. Blood cultures are negative except when secondary invasions occur close to the time of death. The lesion occurs on both sides of valves. Necrosis may occur but not ulceration or perforation of valvular flaps. The valves of the right side of the heart are more frequently involved than those of the left. Mural involvement occurs frequently, even in the right auricle. In examining hearts it is necessary to turn up all the flaps and inspect the valve pockets carefully, because involvement of the valve pockets is characteristic and may be the only evidence of the lesion.

Gradually over a number of years, the subject became clarified. The studies made by Dr. Sacks and me indicated that there existed a disease which could be accompanied by lupus erythematosus or not. Then it was known that lupus erythematosus may occur without any macroscopic evidence of endocarditis. It was suspected that the disease could occur with or without endocarditis. In a paper read at a meeting of the Association of American Physicians in 1938, I put it as follows: "In other words, we have here a general disease in which there may be present the endocardial vegetations alone, the lupus erythematosus alone, both conditions, or neither."

In 1932, Dr. Louis Gross made a careful study of this form of endocarditis and found certain histologic lesions that he considered to be of diagnostic value. In 1936 he attacked the problem again by studying the endocardium and pericardium in cases of lupus erythematosus in which a macroscopic endocarditis was

absent. In most of the cases he found the same histologic lesions which he had noted in 1932 in a study of macroscopic atypical verrucous endocarditis. Cases of the disease without any cutaneous eruption are now recognized on clinical grounds by the presence of the characteristic microscopic lesions of Gross and the presence of the wire loop glomerular lesions (Klemperer).

Of great interest is the paper published by Friedberg, Gross and Wallach in 1936. They described 4 cases characterized by prolonged fever, deforming arthritis, involvement of serous membranes and widespread vascular lesions. In 1 case a rather general adenopathy occurred. In all of the cases there was present a nonbacterial thrombotic endocarditis but no atypical verrucous endocarditis. The authors suspected that these cases were instances of Libman-Sacks disease. After Dr. Gross had defined the characteristic histologic changes in the endocardium and pericardium, which may be present in the absence of any macroscopic evidence of atypical verrucous endocarditis, a restudy of the material still available from 2 of these cases of febrile deforming arthritis revealed the diagnostic microscopic lesions of Gross. These cases were thus proved to be instances of Libman-Sacks disease.

It is important to say something about the general concept of endocarditis. Physicians have not been careful in distinguishing endocarditis from a clinical standpoint and from a pathologic standpoint.

In acute bacterial endocarditis there is often present an extensive primary lesion, such as osteomyelitis, puerperal infection or lateral sinus thrombosis. If the primary focus is still active, the clinical picture is due to both. It is only in the unusual cases in which the primary lesion is slight in extent or already healed that one is dealing with endocarditis as the whole clinical picture. In subacute bacterial endocarditis all the clinical phenomena are due to the endocardial lesion. The same holds true if the infection takes place in an artery (bacterial aortitis, for example) or in a preexisting arterial or arteriovenous aneurysm. The primary focus is never significant.

In rheumatic fever there is an entirely different story. Here is a disease in which a variety of structures may be involved, alone or in various combinations. But whatever structures are specially involved, the background is always the general disease—rheumatic fever. There may be present valvulitis with secondary endocarditis, myocarditis, serositis, synovitis, pulmonary lesions or myositis. Arteritis is uncommon. In the kidney a vascular glomerular lesion may occasionally occur as a diffuse glomerulonephritis. If the brain is involved, the picture is chorea or encephalitis. If the skin is involved, one finds subcutaneous nodules or erythema marginatum. Adenopathy, if ever present, must be very rare.

Libman-Sacks disease, like rheumatic fever, is a disease which may or may not be accompanied by certain clinical features. There may be present an endocarditis with possible secondary valvulitis. But endocarditis may be absent. Nothing definite is known about myocardial involvement, but there is evidence that indicates that it may be present. Serositis and synovitis occur frequently. Arterial involvement occurs often but may be absent. The same holds true for vascular glomerular lesions and diffuse glomerulonephritis. Lesions in the lungs are present in nearly all cases and often appear early. Peculiar cerebral symptoms may occur, such as convulsions, attacks of stupor and palsies. If the skin is involved, the picture is that of dermatomyositis, scleroderma and, much oftener, lupus erythematosus. The lupus may occur early and disappear or persist, or it may appear only in a second or third occurrence of the disease or only shortly before death. It may be absent throughout the disease, even when the latter is characterized by a very prolonged course. It may be present with atypical verrucous endocarditis or alone.

Adenopathy is characteristic of the disease. It may occur early. The nodes may be discrete, moderately or greatly enlarged or in large packets. The histologic picture varies. It may present an appearance like that of an ordinary

hyperplasia or resemble giant follicular lymphoblastoma or Hodgkin's disease, and there may be present the hematoxylin-staining bodies of Gross or macroscopic necroses.

Some time ago I made up the following tabulation to show what is known of the nosologic relations of Libman-Sacks disease.

Libman-Sacks Disease—Nosologic Relations

1. Visceral lesions of the erythema group (Osler syndrome)
2. Rheumatic fever
3. Arthritis deformans and infectious arthritis
4. *Still's Disease* (?)
5. Diseases of lymph nodes
6. Myositis and dermatomyositis
7. Scleroderma
8. Glomerulonephritis
9. Purpura hemorrhagica
10. Necrotizing arteritis (periarteritis nodosa?)
11. Discoid lupus

As regards the Osler syndrome, I will only say that at least 2 of the cases described by Osler have to be reclassified into the new group. This is contrary to the opinion of Belote, who believed that cases of what he called "Libman-Sacks syndrome" belonged to the Osler group. I shall not discuss fully tonight the difficult question as to conditions under which discoid lupus may become generalized lupus. Many dermatologists believe that they have observed such transformations.

The tabulation shows that some conditions formerly considered to be unclassified forms of diseases of lymph nodes belong in this category. The same holds true for some examples of dermatomyositis, scleroderma, glomerulonephritis and purpura haemorrhagica. Some conditions formerly diagnosed as rheumatic fever belong here. Necrotizing arteritis (so-called periarteritis nodosa) may occur in a number of diseases, including rheumatic fever, bacterial endocarditis and this disease.

You will note that I placed Still's disease in the list, although I had not yet obtained definite proof that some examples of this disease belong in the group Libman-Sacks disease.

You can realize how interested I was when Dr. György presented his views to me. I believe that he is on the right track. It is important to observe carefully all cases of infectious arthritis and Still's disease and try to obtain definite proof by finding the macroscopic atypical verrucous endocarditis, the characteristic histologic lesions of Gross or the wire loop glomerular lesions.

Experimental and Clinical Observations of Bacillus Parapertussis. Dr. William L. Bradford, Rochester, N. Y.

During the routine examination of positive cough plate cultures for Haemophilus pertussis, certain strains of an atypical organism were observed. Eight (5 per cent) strains were collected in a series of 160 consecutive positive cultures from persons suspected of having clinical pertussis. Biochemical and immunologic studies proved that these strains were identical. A distinguishing reaction was the production of certain changes of color when the organisms were grown on iron-containing mediums of certain types.

These strains were also found to be identical with those of a group simultaneously observed by Dr. Pearl Kendrick, who named the organism Bacillus parapertussis. Another strain sent by another worker as H. pertussis was found to be of this type.

The morphologic, biochemical, immunologic and clinical attributes of the organism are described in part, and its relation to H. pertussis is briefly discussed.

DISCUSSION

Dr. L. Emmett Holt Jr., Baltimore: I should like to ask Dr. Bradford if he noticed any clinical peculiarities in these cases of parapertussis.

A year ago last winter there were some cases of parapertussis in Baltimore. They were few but seemed to be characterized by a much more rapid period of defervescence than is characteristic of parapertussis.

Dr. Edward M. Bridge, Baltimore: While I am not competent to discuss the bacteriology of parapertussis infections, I have had an experience similar to Dr. Bradford's with an epidemic of 5 cases in my own family. A year later another 5 was recognized in the family of another Baltimore physician. As Dr. Bradford has pointed out, the disease resembles mild pertussis, and in none of the cases would it have been diagnosed except for the curiosity of physician parents and the bacteriologic interest of Dr. Howard Brown. The disease seemed to start in the same way that ordinary pertussis does but quickly faded away at the time when whooping and vomiting should have been starting.

Dr. Horace Hodes suggested that cultures be obtained from the nasopharynx and that the culture swabs be placed immediately in broth until ready for plating. This method proved more satisfactory than the usual cough plate technic.

I was interested in Dr. Bradford's observations on cross agglutination between the two diseases. I made a rather unsatisfactory attempt to demonstrate this and obtained no clear results. A year later 2 of the children contracted true pertussis, having had no prophylactic injections. Both had the disease in such a mild form that it would hardly have been recognized had cultures not been taken. I should like to ask Dr. Bradford whether the pertussis which followed parapertussis in 2 of his cases was also mild and, if so, whether some degree of cross immunity could be inferred.

Dr. William L. Bradford, Rochester, N. Y.: In order to conserve time, I omitted a description of the clinical course of parapertussis. The fact that practically all of the strains that have been isolated have come from children suspected of having whooping cough in itself indicates that the two diseases closely resemble each other in their early stages.

Dr. Holt called attention to the fact that parapertussis begins rather suddenly and perhaps a bit more forcefully than does pertussis. I think I have observed that also. I am sure it was true in the case of my son's illness.

Nineteen strains have to date been isolated. In the majority of instances the children coughed for about two or three weeks. The course was usually mild, without complications, and I have not observed the tendency of the cough to recur when a subsequent infection of the respiratory tract occurs, as is so often observed in pertussis.

Dr. Bridge and I apparently have a mutual claim to authority on the course of the disease because we have both witnessed it in our respective families! In answer to his question concerning cross immunity I can only cite the report of Miller who observed 2 patients with parapertussis in whom typical pertussis developed seven and twelve months later, respectively. I think this observation, if extended, would indicate a failure to immunize against pertussis with an antigen prepared for Bacillus parapertussis. There seems to be little or no evidence of cross immunity, although an antitoxin prepared by inoculating rabbits with Haemophilus pertussis toxin has been found by Evans to neutralize the toxin of B. parapertussis.

Final Session

Saturday Morning, May 2

Premature Cranial Synostosis. Dr. H. K. Faber and Dr. E. B. Towne (by invitation), San Francisco.

Premature synostosis of the cranial sutures, especially the coronal and sagittal, leads not only to severe deformity of the head but to increased intracranial pressure, which in over 90 per cent of patients with oxycephaly causes loss of vision, complete in many cases, and eventual mental deterioration. Loss of vision

in the majority of cases begins before or during the third year. Similar difficulties also occur with scaphocephaly, although blindness and mental deterioration are less common.

The cause of increased intracranial pressure and its sequelae is essentially a disparity between the space required for normal brain growth and the intracranial space, which is prevented by synostosis from increasing *pari passu* with the brain. A sharp distinction exists between this anomaly and the conditions in primary atrophy of the brain, in which the cranium is small but accurately fits a small brain and the sutures do not close at an early period of life.

It has been general practice merely to attempt alleviation of the disturbances caused by premature synostosis, after they are present and usually advanced, by various decompressive operations rather than to employ preventive measures. The results of such late intervention have not been conspicuously good. Vision rarely returns to normal. The most rapid period of growth of the brain and skull is during the first six months of life; during the first year approximately half of the total expansion of the skull occurs. In synostosis the thinness and pliability of the skull during the first year or so permit enough expansion to occur, at the cost of severe deformity, to prevent great increases in intracranial pressure and thus blindness; but with the increasing thickness of the bones and the loss of reserve expansion, blindness becomes increasingly frequent thereafter.

In 1923 one of us proposed that the sequelae of synostosis were frequent and severe enough to justify attempts at prevention. It was suggested that linear resection of cranial bone parallel to the line of abnormal closure might be of value in permitting expansion of the skull in more normal directions and degree and that this should be done when the growth of the brain is at its most accelerated period; preferably by the age of 6 months. In 1924 the operation was performed on a child of 6 months with closure of the sagittal sutures and incipient closure of one of the coronal sutures; the early results were reported in 1927, and the later results, up to 1941 when the patient was 17 years old, are reported in the present paper. A few other cases followed for shorter periods are also reported. The results are considered to be sufficiently encouraging to justify recommendation of the operation in suitable cases.

Polyostotic Fibrous Dysplasia. Dr. D. J. McCune and Dr. John Caffey, New York.

In 1922 Weil described the occurrence in a young girl of a syndrome characterized by precocious puberty, brown maplike pigmentation of the skin and a disposition to repeated pathologic fractures of the long bones. In 1936 McCune and Bruch presented an example of this constellation to the Society for Pediatric Research and reviewed the literature, which was found to contain approximately 15 cases, all but 3 of the patients being children. In the following year Albright, Butler and their collaborators drew attention to the frequency of occurrence of the triad in adults. In 1938 Lichtenstein, on Jaffe's suggestion, emphasized the relation between the complete syndrome and the forms in which the skeletal peculiarities alone are manifest. Lichtenstein coined the designation which we have temporarily adopted. At the present time the literature contains approximately 40 recognizable examples, to take no account of the undoubtedly much larger number of cases which have been reported under such a variety of titles and details as to make their discovery difficult and their identification impossible.

The common denominator in these cases is the osteologic congruence. Under the microscope this expresses itself through regressive metaplasia of bone into dense fibrous and fibroblastic tissue; sometimes masses of cartilage are present. The roentgen features are those of diffuse and focal decrease of density associated closely with areas of what appears to be osteosclerosis. The process, although widely disseminated, is not generalized; asymmetry, sufficiently pronounced to justify the characterization unilateral, is sometimes encountered. Pathologic fractures and progressive coxa vara are the most common overt manifestations. The two sexes appear to be equally affected. Both males and females may show the

characteristic maplike pigmentation, which is usually present at birth; puberal precocity is limited to females.

Causation remains obscure. Interpretable hormonal peculiarities have not been demonstrated; significant lesions of the endocrine glands have not come to light at autopsy. Inquiry into genetic causes is blocked by the entire absence of reports of hereditary or familial cases.

The description of 5 new cases illustrates the considerable variety of combination and degree of severity which may be encountered and directs attention toward the differential diagnosis. This must include virtually all cystic and pseudocystic diseases of bone, especially osteitis fibrosa cystica, xanthomatosis, neurofibromatosis, cystic tuberculosis of bone and eosinophilic granuloma.

Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency. Dr. Josef Warkany, Dr. Rose C. Nelson (by invitation) and Dr. Elizabeth Schraffenberger (by invitation), Cincinnati.

This paper will be published in full in a later issue of the American Journal of Diseases of Children.

Effects of Various Androgens on Sexually Immature Dwarfs. Dr. Lawson Wilkins, Dr. Walter Fleischmann (by invitation) and Dr. John E. Howard (by invitation), Baltimore.

Sexually immature male dwarfs aged 16 years or older were treated with 25 mg. of methyl testosterone by mouth daily. The average rate of growth increased from 1 inch (2.5 cm.) to 5 inches (12.5 cm.) per year. Osseous development progressed at a more rapid rate than previously, but there was no sudden closure of the epiphysial lines. The weight and musculature increased. The treatment caused a definite retention of nitrogen, which was manifested within one to three days. The excretion of creatine increased after a latent period of ten days or more and remained elevated under treatment for periods of a year or more. Irregular elevations of the basal metabolic rate were encountered in patients under treatment. Pronounced creatinuria occurred also when methyl testosterone was administered intramuscularly instead of by the oral route. Creatinuria and irregular elevations of the basal metabolic rate occurred when methyl testosterone was given to a cretin, which proved that these effects are not dependent on the thyroid gland.

Sexually infantile female dwarfs treated with 1 mg. of diethylstilbestrol by mouth daily did not show retention of nitrogen or creatinuria. The addition of 25 mg. of methyl testosterone to the treatment with stilbestrol caused both retention of nitrogen and creatinuria, as in the males. One female dwarf given the combined treatment for a year grew and showed excellent sexual development without virilization. Another showed slight virilization after four months, so that treatment was discontinued.

A quantitative comparison of the nitrogen-retaining effects of methyl testosterone and testosterone propionate is difficult, but there were suggestions that methyl testosterone might be more effective in this respect.

In the hope of finding substances capable of causing retention of nitrogen and growth but having little androgenic effect, the following steroids were studied: androsterone, transdehydroandrosterone, androstenedione, androstenediol and ethinyl testosterone (anhydrohydroxyprogesterone). In the doses administered, none of these caused retention of nitrogen or creatinuria.

Adrenogenital Syndrome: Diagnosis, Course and Treatment. Dr. Nathan B. Talbot, Dr. Allan M. Butler ad Dr. R. A. Berman (by invitation), Boston.

The total urinary excretion of 17-keto steroids is higher in patients with corticoadrenal hyperplasia or corticoadrenal carcinoma than in patients with any other type of disease thus far encountered. Therefore, assay of the total output of

17-keto steroids is of value in the diagnosis of corticoadrenal hyperactivity. However, the magnitude of the total excretion of 17-keto steroids is not always a reliable index of the exact nature of this hyperactivity. On the other hand, the output of the beta alcoholic and the nonalcoholic 17-keto steroids has been found to be abnormally increased only in patients with corticoadrenal carcinoma. Assay of the excretion of the latter two fractions therefore appears to be of diagnostic value in differentiating patients with corticoadrenal hyperplasia from those with corticoadrenal carcinoma.

In agreement with the observations of others, the values of urinary pregnandiol are not consistently elevated in patients with corticoadrenal hyperplasia. Hence they do not appear to have diagnostic significance in that disease.

The adrenogenital syndrome when due to hyperplasia of the adrenal cortex is a disease which usually progresses without a tendency to spontaneous remissions. Children of both sexes may tend to be unusually tall at the onset of the disease but will probably cease growing at an abnormally early age because of premature closure of the epiphyses. There is a probability that the boys will become normal-appearing men, and there is a possibility that they will mature. If left untreated, the girls tend to remain chronically masculinized.

The treatment of choice for patients with a carcinoma of the adrenal cortex is surgical removal. On the other hand, surgery is not indicated in the treatment of patients with the adrenogenital syndrome due to corticoadrenal hyperplasia. In girls with the latter disease, orally administered diethylstilbestrol causes a pronounced improvement in the physical appearance and psychologic outlook. On the other hand, there appears to be little indication for such therapy for boys.

DISCUSSION

DR. JOSEF WARKANY, Cincinnati: The differential diagnosis in cases of precocious puberty is very difficult, since in addition to adrenal hyperplasia and benign and malignant tumors of the adrenal cortex gonadal and cerebral sexual precocity have to be considered.

In several cases in which my colleagues and I were at a loss as to diagnosis and prognosis, Dr. Talbot has been kind enough to assay urines of the patients for us. The amounts of 17-keto steroids excreted permit certain conclusions, as Dr. Talbot has pointed out. So far his interpretation of the urinary assays has been in agreement with the clinical course in every case. It seems that these methods will be of great practical importance to any one who takes care of children with precocious puberty.

DR. LAWSON WILKINS, Baltimore: I am afraid I can add nothing to what Dr. Talbot has said except my extreme admiration for his work. I was especially interested in his observation that in sexual precocity of adrenal origin the testes may develop entirely normally at the age of puberty. I had believed that sexual precocity occurring in a boy with small testes was due to adrenal hyperplasia or tumor, whereas in a boy with well developed testes it usually was due to a cerebral or pituitary type of stimulation. He has shown, however, that after a patient reaches the age of puberty one cannot make the differentiation by the size of the testes.

DR. IRVINE MCQUARRIE, Minneapolis: I too should like to congratulate the authors of these two papers on their beautiful work. I should like to refer to 3 cases of what was apparently the adrenogenital syndrome presented by Dr. Albert Kaiser some fifteen years ago before a clinical conference in Rochester, N. Y. The patients were brothers, aged 5, 7 and 9 years at the time. Hyperplasia of the androgenic zone of the adrenal cortex (rather than carcinoma) must have been the inciting cause of the macrogenitosomia praecox. When I inquired about these patients recently, Dr. Kaiser informed me that they are all living and well and appear to be normal in every way. No special treatment was given. This confirms Dr. Talbot's conclusion that pathologic conditions of this type without tumor should be treated conservatively.

There is another type of hypercorticoadrenalism with Cushing's syndrome which I have discussed in the paper listed on this year's program under the

heading "Read by Title." In contrast to the hyperfunctioning of the androgenic zone observed in cases of macrogenitosomia, there is primarily an overactivity of other cortical cells, producing changes in the serum electrolytes which tend to be the reverse of those occurring in patients with Addison's disease. I have found these changes in cases of adrenal carcinoma and also in cases of simple cortical hyperplasia with little or no genital or skeletal precocity. The urinary levels of the 17-keto steroids tend to be increased somewhat, but not so strikingly as in the cases just described. I first reported the characteristic changes in cases of this type in 1937. Kepler and his associates have since reported similar alterations in the serum electrolyte pattern in adult patients with adrenal cortical hyperplasia. Only in exceptional cases of the Cushing syndrome, however, are these blood changes shown.

DR. NATHAN B. TALBOT, Boston: I should like to take this opportunity to thank the many physicians who have been so kind as to send us samples of urine and case summaries for our benefit. Without this help it would have been impossible to accumulate even this small series of data from our local community.

With respect to Cushing's syndrome, it would seem that the determinations of 17-keto steroids were as valid in a differential diagnosis of adrenal cortical hyperplasia and adrenal cortical carcinoma in cases of that syndrome as in those of the adrenogenital syndrome.

I think Dr. Wilkins' contributions are important and open up new opportunities for therapy which will probably be of considerable interest to pediatricians. However, this new type of treatment is still in the experimental stage, particularly for younger patients. In other words, although methyl testosterone and other related compounds are extremely potent and efficacious, they may have certain undesirable side effects. Therefore, except for experimental purposes, it may be desirable, at least for the present, to reserve this type of therapy for patients who clearly need it.

The Heart in Chorea. DR. STANLEY GIBSON and DR. ROWINE M. HAYES (by invitation), Chicago.

Many theories have been advanced concerning the nature of chorea. A few investigators have regarded it as a functional disease of the nervous system, the chief etiologic factor being fright or other psychic trauma. Others have regarded chorea and rheumatic fever as separate entities but occurring in children of a similar constitution. The majority have regarded chorea as a rheumatic manifestation, but there is difference of opinion as to the importance of chorea in the causation of rheumatic heart disease.

In a series of 640 cases of chorea, we have encountered 90 cases in which chorea and heart disease coexisted in the absence of other rheumatic phenomena. We have made a clinical study of these cases to determine the time of onset of the cardiac disturbance, the nature of the valvular involvement, the severity of the injury to the heart and the incidence of recurrences.

Definite signs of cardiac involvement were seldom found during the active course of the chorea. The heart often remained normal for months or years; then, in the absence of any intervening illness, signs of mitral stenosis appeared. An aortic lesion was found in only 9 instances. Mild cardiac failure occurred in only 2 patients. During the period of observation there was no mortality.

These observations suggest that chorea is an important rheumatic manifestation, often followed by rheumatic heart disease. The cardiac involvement is, however, much less severe than that which follows rheumatic polyarthritis.

DISCUSSION

DR. HUGH MCCULLOCH, St. Louis: Dr. Gibson has accumulated a large amount of material to show the relation of chorea to the problem of rheumatic fever and rheumatic heart disease. I had hoped there might be some new point that would solve this problem, but, except for the statistical probability of relationship, the matter is still uncertain. Rheumatic fever remains a disease which has a limited approach by scientific study.

DR. STANLEY GIBSON, Chicago: The point that we have particularly tried to emphasize is that there is a relatively small group of patients whose sole rheumatic manifestations are chorea and heart disease and that in this group the cardiac manifestations are of a somewhat different order than those ordinarily encountered.

Anxieties in Children: Their Cause and Implications. DR. BERT I. BEVERLY (by invitation), Chicago.

This paper will be published in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Relation of the Retention of Nitrogen and Calcium to the Development and Course of the Reinfection Type of Tuberculosis in the Adolescent. DR. J. A. JOHNSTON, Detroit.

Approximately 1,000 children who gave a positive reaction to tuberculin and were removed from contact have been followed for about twelve years after removal from contact, and there has been reported before this society the development of presumably endogenous reinfection in about 3 per cent of the group. On the discovery of the reinfection, these patients were hospitalized and placed on measured diets and the balances were determined for nitrogen and calcium. The caloric content of the diets was dictated largely by the child's appetite, though once determined in this way it usually remained fixed throughout the observation unless otherwise noted. Fifteen per cent of the calories derived from protein, and the calcium content of the 2,000 calory diet averaged 1.16 Gm. One of the items of study was the effect of varying these factors and the intake of vitamin D; this item was omitted unless a part of a special study. Diets were analyzed every six days, one sixth of a duplicate diet being set aside daily for this purpose.

It was the thought of my colleagues and me that the pattern of the retention of these structural substances might furnish evidence of previous depletion not apparent in the weight curve, and we hoped too to obtain correlations between these patterns and the healing process or progression of the disease. But because we were also conscious of the fact that numerous other factors than the intake determined retention, studies were also made of a number of these which might play a role. Among them, diet, puberty in the girl, at least two of the hormones —the thyroid hormone and estrogen—and focal infection were shown to be items which depressed retention and might conceivably influence a depletion which conditioned the development and possibly the course of the disease. It is recognized at the outset that an obvious objection to this approach relates to the difficulty of distinguishing between the effect of the disease, even when detected in the minimal stages, as was possible in this study, before it had given rise to fever, and the state of depleted stores resulting from one of the factors mentioned. However, with this qualification in mind in interpreting them, there are presented a number of continuous balances which show the pattern of the retention of nitrogen and sometimes of calcium, first, during uncomplicated recovery from minimal lesions, and, second, in a number of instances in which the course was complicated by spread.

The balances of 5 adolescent girls whose minimal reinfections healed uninterruptedly were recorded for periods averaging two hundred days. Similar though longer records were compiled of 4 patients whose initial progress was interrupted by spread.

In general, these observations suggest that the healing of the reinfection type of tuberculosis in the adolescent is accompanied by the steadily increasing retention of nitrogen and calcium up to a high point suggestive of saturation of depots previously depleted and that spread is accompanied by low or negative balances for these items. We have the impression that this metabolic state may condition rather than be the result of the spread. It is pointed out that a variety of factors, dietary, endocrine and others, may play roles in influencing unfavorably the course of the lesion and that all of these may exert their effects by the production of negative balances for elements essential to healing, of which nitrogen and calcium are examples.

Book Reviews

From Infancy Through Childhood. By Louis W. Sauer, M.D., Ph.D. Price, $2.00. Pp. 200, with 13 illustrations and 5 charts. New York: Harper Bros., 1942.

Dr. Sauer has written a small (190 page) book for mothers which will fill a definite need. The chapters are on the prenatal and newborn periods, breast feeding, bottle feeding, vitamins and balanced diets, physical health, mental health, common noncontagious diseases, common contagious diseases, the prematurely born infant, the adopted child, accidents and poisons and antidotes.

These subjects are dealt with briefly, so briefly that the mother who does not read much will find no difficulty in reading the book through and in using it for reference. There is a large field of usefulness for a volume that covers the subject of infant and child care in such an easy and readable manner.

Necessarily, the space for discussion is very limited. This is particularly felt in the consideration of minor bad habits in the chapter on mental health. Here lying, masturbation, temper tantrums and other such habits are dealt with so briefly that it is impossible to be sure that any real understanding of the condition has been conveyed to the mother. This is, however, compensated for by the often repeated advice to consult the physician in case of any difficulty.

In reviewing any book there is always the temptation to emphasize differences of opinion in details. This reviewer would not agree with Dr. Sauer in listing scarlet fever immunization as always desirable or in not advising tetanus immunization. It also seems unwise to advocate the regular use of convalescent serum or antitoxin in cases of scarlet fever and the use of convalescent serum for poliomyelitis. The use of serum in the treatment of disease need not be discussed in a book for mothers, and it is at least debatable whether serum should always be used in scarlet fever and whether it should be used at all in poliomyelitis.

The book has the decided advantage that it touches on more phases of child health and is thus more nearly complete than any other book of its size, and any intelligent mother who is looking for more information on any particular subject should be stimulated to look for a specialized and more detailed study. This volume will be helpful to young mothers and will be popular.

Diabetes Mellitus. By Zolton T. Wirtschafter, M.D., and Morton Korenberg, M.D. Price, $2.50. Pp. 186, with 9 illustrations and 3 tables. Baltimore: The Williams & Wilkins Company, 1942.

"Diabetes Mellitus" by Wirtschafter and Korenberg brings many important references up to date. All writers on the subject of diabetes should be encouraged. This is not recommended as a reference book to guide medical students or physicians in the practical handling of problems involved in the treatment of diabetes.

A lack of therapeutic experience on the part of the authors must account for the management of diabetic coma described. If this management were followed to the letter, the mortality of diabetic coma would be nearly that of the preinsulin era. Vitamins rather than adequate doses of insulin are advocated by the authors. That diabetic coma is primarily a state of insulin insufficiency is completely overlooked.

The fact that the most recent physiologic experiments in low carbohydrate diet are interpreted to favor regeneration of the islet tissue has been overlooked, and such diets are described by the authors as diabetogenic. The value of protamine zinc insulin in controlling nocturnal hyperglycemia has not been recognized.

Only brief mention is made of the important subject of juvenile diabetes.